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CLINICAL STUDIES IN CAFFEIN*

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The pharmacological action of caffein as it relates to the normal man and animal has been for many years the subject of extensive research. Its main effects on the normal cardiovascular and nervous systems are well known. Briefly stated for the purpose of this paper, this effect of caffein in moderate doses is, first, to produce a moderate rise of blood-pressure due to a stimulant action on the heart muscle (this rise is maintained in spite of a mild degree of vasodilatation); second, an increased urinary output due to circulatory changes, and third, an increased respiratory rate. The cerebral functions are stimulated and the muscle tone increased. This experimental field was reviewed and the varying results of the different investigators harmonized by Sollmann and Pilcher[1] in 1911.

With this action in mind the pharmacologists have given the drug a high therapeutic rating and it has been extensively used as a cardiac and nerve stimulant. It is one thing to inject a drug directly into the blood-stream of an animal with a normal circulatory system or again into an animal under the influence of an anesthetic and the surgical procedures necessary for the recording of blood-pressure, variations in the size of the kidney, etc.; and quite a different thing to give a drug by mouth, in the usual clinical way, where the absorption is more or less delayed and in cases in which the cardiovascular system is not intact. In one case the results may be prompt, definite, limited; in the other case they may be slow to appear, indefinite, and continued

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* This investigation was undertaken at the suggestion of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

1. Sollmann, T., and Pilcher, T. D.: The Actions of Caffein on the Mammalian Circulation, Jour. Pharm. and Exper. Therap., 1911, iii, 19.

in their action. In the animal the distressing symptoms caused by the drug are beyond the reach of the investigator to determine; in the sick man these assume paramount importance. With the idea of further testing the effect of caffein on the pathological circulatory system of the human being, and if possible adding to our clinical knowledge of the drug, these observations were made.

The patients chosen were all adults, the youngest 24, the oldest 56, suffering from advanced myocardial disease. In some cases the myocardial insufficiency was primary, in others secondary to a chronic nephritis or an old endocarditis. The fifteen cases reported were selected because in these cases the observations were fairly complete. In numerous other cases the loss of specimens, death, or intercurrent complications requiring the use of other therapeutic measures made the analysis of caffein action impossible. Every case showed some sign of broken compensation at the time of the experiment, and thirteen gave evidence of retained body fluid. Dyspnea was present in 14 cases; edema of the extremities in 13 cases; ascites in 10 cases; hydropericardium and hydrothorax, single or double, in 6; tender pulsating liver in 6. Other common symptoms were cough, frontal headache, weakness, dizziness and substernal pain.

All patients were kept in bed on a constant diet. Milk with the possible diuretic action of its milk-sugar was eliminated in all but one case, and here milk had been a constant factor in the diet for several days previous to the administration of the drug. No effort was made to reduce the salt intake. The fluid intake was measured and in eleven of the fifteen cases was kept constant at amounts varying in the different cases from 930 to 2,100 c.c., depending on the wish of the patient. The patient was allowed to use what water he wanted on the first day, and that amount was taken as a constant for subsequent days. The average intake was 1,200 c.c. No medication or depleting therapy of any kind was allowed for four days preceding the experiment, so that rest as a factor in restoring cardiac function might come as near as possible to a constant level.

In eight cases citrated caffein was used in doses of 10 grains, four times daily. In Case 2, in which there was no noticeable result with that dosage, it was pushed to 100 grains a day. In two cases the dose was reduced to 5 grains, three times a day. The average of the eight cases was 32.5 grains a day of the citrate, which is the equivalent of 16.25 grains of the pure caffein. In seven cases the pure alkaloid, caffeina, was used in doses of 3 to 5 grains, four times daily; an average of 17.7 grains per day. The drug was discontinued usually because of the appearance of unpleasant symptoms. The average use of the citrate extended over 4.8 days, that of the pure drug, 4.6 days, so that

both the dosage and the length of time during which the different preparations was used were practically the same.

Effect on the Pulse-Rate. — The pulse was taken one-half hour before and again one-half hour after the administration of the drug. The rate previous to giving the drug was taken as the gauge of a permanent drug effect, and in this series of observations showed no definite change. In six cases there was a permanent rise of five beats a minute, or 7 per cent., but in eight others there was a drop of 7 per cent., so that these variations fall well within the limits of chance disturbances. In one case an intercurrent febrile attack sent the pulse-rate up, invalidating the result. The maximum effect on the pulse-rate appeared in one-half hour and consisted of a temporary rise in every case, varying from 2 per cent. in Case 6 to 5.7 per cent. in Case 10. The average rise was 3.6 per cent. This rise, it is true, is relatively small, but in this series constant and for that reason worth noting. In none of these cases was there a tachycardia, the pulse ranging from 70 to 90. This fact combined with the relatively small temporary rise made it impossible to make any clinical comments on the fact noted in dogs that caffein causes a greater quickening in hearts which have a high rate. Certainly we may say that in this group of cases caffein has no permanent or clinical effect on the heart-rate.

Effect on the Respiratory Rate.—This was determined, as was the pulse-rate, by observations one-half hour before and after the administration of the drug, a total of eight readings a day. Even in cases with dyspnea and the relief of that symptom, the change in the rate could not be ascribed to the action of the caffein directly on the respiratory center, but rather to a secondary action through improvement of the circulation. In cases without dyspnea or in the cases in which the dyspnea had subsided, there was no effect, permanent or temporary, which could be clinically determined.

Effect on the Blood-Pressure.—The pressure was measured usually at 10 a. m. with a 10 cm. cuff, Riva-Rocci, by the auscultatory method. Chart 1 gives the pressure from day to day in each case, and in Chart 2 is given the composite curve of the fifteen cases. In twelve of the cases there was a marked drop in the pressure varying from 8 mm. in Case 12 to 50 mm. in Case 15. In Case 10, in which the endocardium was mainly at fault and there was little stasis, the blood-pressure remained at 135 mm. systolic. In Case 9 a pressure of 120 rose at first to 140 under caffein, but later dropped to 112 mm. In Case 3, in which the largest dosage was used, a case of luetic myocarditis confirmed at necropsy, the pressure rose under 100 grains of caffein daily from 172 systolic and 125 diastolic to 192 systolic and 150 diastolic. In three cases the drop was between 40 and 50 mm.; in three cases

between 30 and 40; in three cases between 10 and 20, and in three cases below 10. The mean curve shows a slight drop the first day and a well-marked drop the second and third day with a gradual fall thereafter, the fall averaging about 2.5 mm. per day. That there is good clinical evidence that this drop in blood-pressure is due partly at least

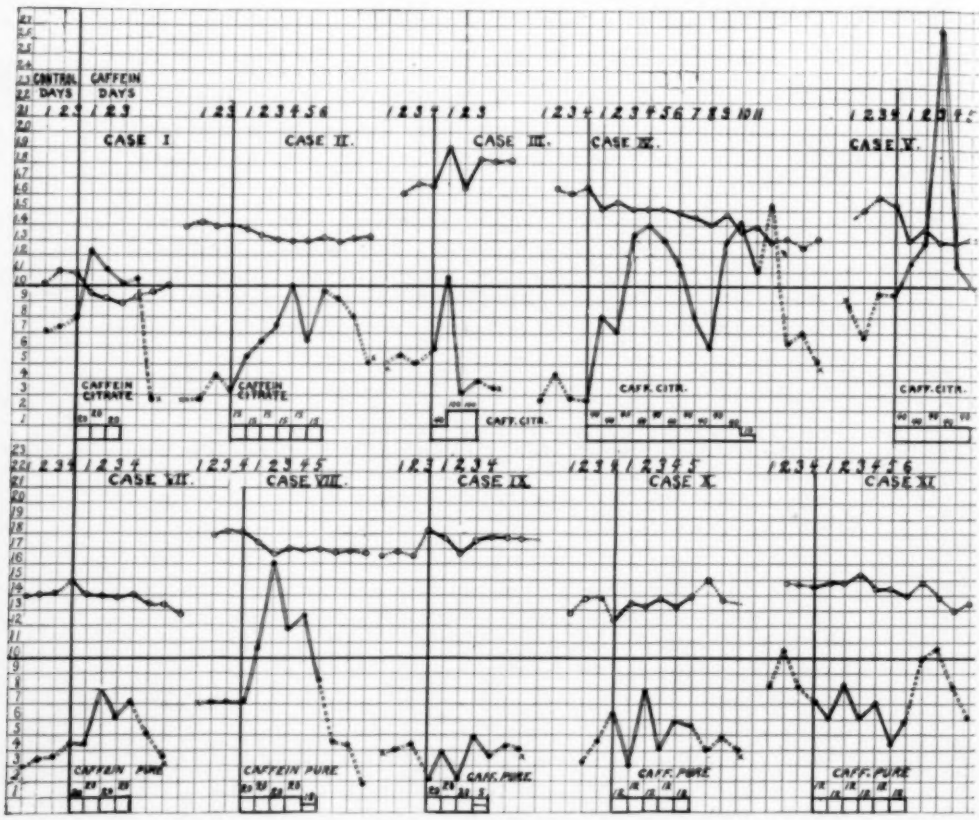
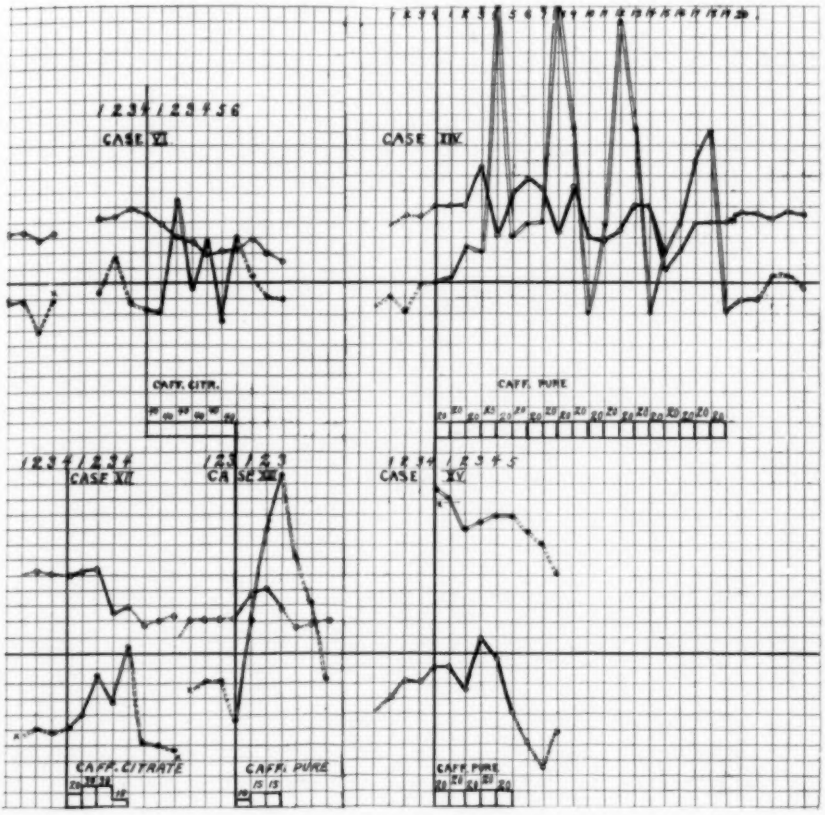


Chart 1. — Individual curve of blood-pressure (o --- o --- o — o — o) and diuretic coefficient and after the drug. The base line corresponds to a diuretic coefficient (output of urine divided by sure of 110 and diuretic coefficient of 1.1, etc. The dosage refers to grains per day of either citrated

to a peripheral dilatation of the vessels will be discussed later. From the charts then we may conclude that the final effect of caffein on the blood-pressure is to produce a depression, although in a few cases this may be preceded by a temporary rise on the first day. The fall is apt to continue after the administration is stopped.

Effect on Diuresis. — Chart 1 also serves to show the effect of caffein on the "diuretic coefficient." By the diuretic coefficient we mean the relation between the urine output and the fluid intake of the body. In the charts given here, for example, a diuretic coefficient of 0.6 means that the urine output equaled six-tenths or 60 per cent. of the fluid



(●═●═●:::●:::●) of 15 patients. Solid lines during caffein; broken lines before income of fluid) of 1.0, and to a blood-pressure of 100 mm. Hg. 1.1 = blood-pres- or pure caffein, as shown on the curve.

intake. So also a diuretic coefficient of 2.8 represents a urine excretion that is 280 per cent. of the intake. The individual cases are shown in Chart 1, while in Chart 2 the mean curve is shown. As plotted here it shows a prompt and sudden jump in the diuretic coefficient, a rise which progresses steadily to its maximum on the fourth day and then

subsides. This return of the urine flow toward the normal is doubtless due to the smaller amount of disposable fluid, as the edema disappears. In all fifteen of the cases there was some rise on the second or third day, although in three of the cases it was not sufficient to be of any clinical importance. In two of these twelve cases the urine output equaled or excelled the fluid intake. It will be noted from the individual curves that while the ascent of the curve is not so marked on the third and fourth day, nevertheless the cases that respond most favorably to the drug show their greatest activity at that time. The less favorable cases show their activity on the first and second day and subside again. In two cases the stopping of the drug produced a secondary rise. In three of the four cases with their maximum on the fourth day the diuretic coefficient was 2.1, 2.7 and 2.8.

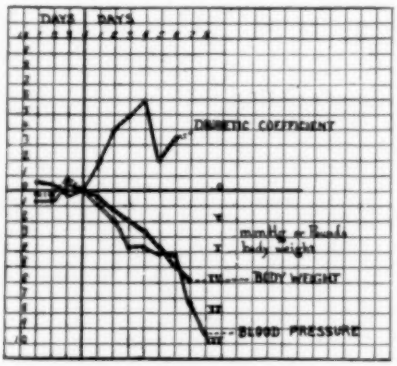


Chart 2.—Mean curves (compiled from the fifteen cases) of diuretic coefficient body, weight and blood-pressure. The base line corresponds to the level when caffein was started. Each square corresponds to a change of 0.1 in the diuretic coefficient, of 2.5 mm. of blood-pressure, and of 2.5 pounds of body weight.

When the mean curves of the blood-pressure and the diuretic coefficient are superimposed, the relation of these two factors seems at least suggestive, the diuresis varying inversely as the pressure. I would recall here the work of Loewi, who demonstrated that diuresis under caffein in the lower animals was due largely to a dilatation of the renal vessels. That there is also a general vasomotor relaxation has been demonstrated, although the cardiac action of caffein is usually regarded as sufficient to maintain or even elevate the blood-pressure. That caffein increases the tone of the blood-vessels is a popular therapeutic idea which animal experiment and clinical observation deny. Taking the cases singly, one finds that the day with the largest drop in the pressure there will also appear the largest urine output. And through-

out, those cases which showed the greatest elimination of body fluid also showed the greatest general drop in blood-pressure. Of special interest was Case 14 in Chart 1. Here are shown very marked oscillations in the curve, the maximum diuretic coefficient appearing at four-day intervals, and associated with a marked drop in blood-pressure. A drop in the systolic pressure from 160 mm. to 130 mm. would be associated with a jump in the diuretic coefficient. This action was probably due to a spasmodic hypertonus, and the relief of the hypertonus could very well be absolutely independent of the caffein, although these blood-pressure changes did not appear until the caffein was begun. In the other cases, however, we did not see such marked action from the caffein on the blood-pressure. It can hardly be explained by the action of caffein on the vasomotor centers, because we find that after caffein the normal irritability is reduced, contrary to

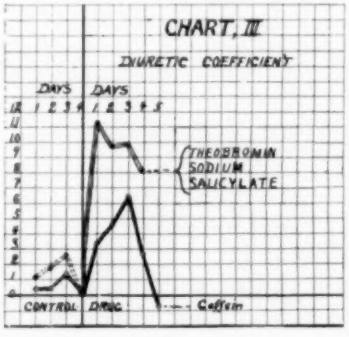


Chart 3.—Comparison of caffein and theobromin sodium salicylate. Mean curve of diuretic coefficient from five patients (3, 6, 7, 9, 13), on whom both drugs were used under similar conditions.

what we might expect from its other cerebral action. We feel, therefor, that the clinical diuretic action of caffein is the result of reduced pressure and vasodilatation.

Effect on the Body Weight.—As is to be expected, the weight decreases with the loss of fluid by the diuresis, so that the curve of the body weight (Chart 2) will be seen to vary inversely as the curve of the diuretic coefficient. These individual curves could not be included with the blood-pressure and the diuretic coefficient without complicating the curves so that they would be unintelligible. Only the composite curve is shown here. The weight of the patient's stool was considered, and in these curves we can tell when the loss of weight is due to the loss of body fluid. The first day shows a small drop which continues steadily, the largest drop occurring in cases in which the

action extended over six or eight days. Three cases, Nos. 6, 9 and 11, showed a small gain in weight up to 4 pounds with increased retention of body fluid, the other cases showing a loss varying from two to twenty pounds consistent with their urine output. Chart 2 shows the relation of the composite curves of the blood-pressure, diuretic coefficient and the body weight after caffein administration and with the four days' control.

Unpleasant Symptoms.—One of the most constant findings was the unpleasant symptoms from the drug. The caffein was given in capsules or powders by mouth, in 3 ounces of water, rather than hypodermatically, in order that its use might correspond to the ordinary clinical administration. These effects were mainly nervous and gastric. In thirteen of the fifteen cases there was discomfort shown from the

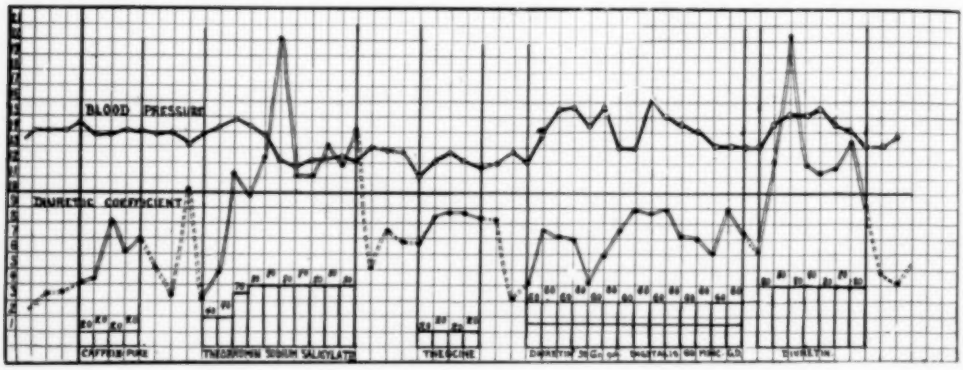


Chart 4.—Comparison of several drugs on same patient (Case 7). The upper curve is the blood-pressure; the lower, the diuretic coefficient. The doses are grains per day.

drug. Eight patients were unable to sleep; seven complained of a vague uneasiness, a sense of restlessness; seven had nausea; five vomiting; four headache; two could not eat, and one besides being unable to eat or sleep insisted that the medicine gave him a pain in the side, the cause of which was not determined. The doses used were full doses, it is true, but no larger than necessary to secure results, and when they were reduced below the point where they gave nervous phenomena their cardiac value had disappeared.

Clinical Efficiency.—Grouping the cases according to their clinical action, the drug has been credited with excellent results, moderate or none, according as it has relieved the subjective symptoms of cardiac origin, caused a diuresis or removed the objective signs. Of the fifteen cases the results were excellent in eight; moderate in four, and there was no result in three. In one of the cases where there was

no result, the vomiting and loss of sleep even on small doses more than balanced any possible good that the drug could have done. All the cases with limited results showed the nervous signs, so the absorption of the drug was assured.

Comparison with Theobromin Sodium Salicylate.—In five of these cases a second admission to the hospital or a return of symptoms while they were still in the institution made it possible to try the comparative therapy of theobromin sodium salicylate under the same conditions and on the same heart on which the caffein action had been tested. Two charts are shown. One, Chart 3, represents two composite curves of these five cases. They show the mean curves of the caffein and theobromin sodium salicylate action on the diuretic coefficient, and are self-explanatory. The other, Chart 4, represents the relative effects of various drugs on the blood-pressure and diuresis in the same case, an old myocarditis. This chart is in accord with the other charts and our clinical experience in demonstrating that, while the action of caffein as a cardiac diuretic may be proved, still it is often of no clinical importance and is very much weaker than the other diuretics.

Our conclusions in regard to theobromin sodium salicylate are that its action on the urinary outflow is more prompt than that of caffein and the diuresis is larger. One can usually tell in twenty-four hours, in a given case, whether theobromin sodium salicylate will act or not; while with caffein the third or fourth day is more apt to show results. The theobromin sodium salicylate action is equally well sustained and usually at a higher level than the caffein. Where caffein has a depressing effect on the vasomotor system and lowers the blood-pressure, theobromin sodium salicylate first elevates the pressure and then later lowers it. The dosage of theobromin sodium salicylate we have found to play an important part in its action. As shown in Chart 4, a dosage of 30 grains daily, even though combined with digitalis, gave but little result; 40 grains daily gave a moderate diuresis, but a vigorous and prompt diuresis is the result of pushing the dose to 80 grains a day. In the chart this fact may be seen at two different points. This has been a frequent clinical experience, so that we regard 80 grains a day as a normal clinical dose. Patients will tolerate this dose easily, and this is an important practical factor in choosing a drug. Not only is the theobromin sodium salicylate action prompter, much stronger and equally well sustained, but we have found none of the gastric and nerve disturbances attendant on caffein. It is useless to give theobromin sodium salicylate in a given case and wait any length of time for its action to appear. In this group of cases with myocardial edema, experience with both drugs demonstrates the decided superiority of theobromin sodium salicylate over caffein. The relative value

of the two drugs in arterial disease, cerebral and coronary sclerosis, is of course an entirely different problem.

Effective Dosage of Caffein.—In cases with edema, the diuretic effect of the drug may be safely taken as a sign of an improved mass movement of blood, which is the result we desire. From this point of view it is evident in this series that the small doses advocated by Romberg are not adequate. The best results were obtained in Cases 4, 5, 6, 8 and 14 with full doses. A good result was also obtained in Case 13 with a smaller dose, but even this dose, from 10 to 15 grains daily of the pure caffein, is much larger than that advocated by Romberg, who uses 2 grains for three doses. Inversely, in the cases with the smaller dose, Cases 2, 9 and 11, there was little clinical value from the drug. By administration by mouth the larger doses must be used to be efficient and almost always at the risk of unpleasant symptoms. The doses were often pushed to the limit of the patient's comfort, but there was no evidence that such doses produced an oliguria or a reversal of the vascular action. The hypodermic use of caffein in acute pulmonary edema and other acute heart conditions as a prompt cardiac stimulant will be taken up in another paper, in which I shall also present findings as to the nature of this caffein diuresis and the action of the drug on renal anasarca. In this series the hypodermic method was not employed, because even in hospital practice so many repeated injections have their disadvantages.

SUMMARY

In myocardial insufficiency with retained body fluid, caffein causes:

1. A moderate increase in the urine output with a proportional loss of body weight. This increase reaches its maximum on the fourth day.

2. A drop in both the systolic and diastolic blood-pressures which may stand in a causal relation to the diuretic coefficient, contrary to the usual teaching.

3. A slight (3.6 per cent.) temporary rise in the pulse-rate, but no permanent change in either the pulse or respiratory rate.

4. A moderate relief of the cardiac symptoms.

5. The constant appearance of distressing nervous and gastric symptoms.

The clinical diuretic action of caffein may be better performed by large doses of theobromin sodium salicylate without the unpleasant side effects.

This preliminary report is presented with a feeling of deep gratitude to Dr. C. F. Hoover and Dr. Torald Sollmann for their generosity with material and constant valuable suggestions in carrying on this work.

POSTANESTHETIC GLYCOSURIA AS INFLUENCED BY DIET, BODY TEMPERATURE AND PURITY OF THE ETHER*

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In 1904 one of us[1] reported the occurrence of glycosuria when meat-fed or fasting dogs were subjected to ether anesthesia for varying periods of time. In the case of the meat-fed animals the percentage of dextrose in the urine fraction first voided after anesthesia ranged from 1.32 per cent. to 6.94 per cent. In the case of the fasting dogs the percentage ranged from a negative test to 0.52 per cent.[2] In 1905 Seelig[3] confirmed these findings. At this time (1904-6) all ethers used for purposes of anesthesia contained aldehyd and other impurities. Recently Prof. Charles Baskerville has succeeded in purifying ethers,[4] and it was he who suggested that we investigate the relationship of this purified or so-called "dehydrated" ether to post-anesthetic glycosuria.[5]

Two other phases of the glycosuria question were incorporated with the study of the glycosuria-producing properties of the "dehydrated" ether, that is, the influence of diet and of the lowering of body temperature on the production of post-anesthetic glycosuria. We shall first discuss the body temperature factor.

I.—RELATIONSHIP OF BODY TEMPERATURE TO GLYCOSURIA

Araki[6] was one of the first investigators to demonstrate that a pronounced lowering of the body temperature of an animal by *external* means caused the appearance of sugar in the urine of that animal. He experimented with rabbits and dogs, using baths of ice-water and of snow to secure low body temperatures. Of five experiments on rabbits three were positive, the urine containing from 0.75 per cent. to 2.5 per

* Submitted for publication June 27, 1914.

* From the Laboratories of Physiological-Chemistry of Jefferson Medical College and the University of Illinois.

1. Hawk, P. B.: Proceedings of American Physiological Society, Am. Jour. Physiol., 1904, x, 37.

2. Hawk, P. B.: Postanesthetic Glycosuria, THE ARCHIVES INT. MED., 1911, viii, 39.

3. Seelig: Arch. f. exper. Path. u. Pharm., 1905, lii, 481, also 1906, liv, 206.

4. Baskerville and Hamor: Jour. Indust. and Engin. Chem., 1911, iii, 1. See also Gwathmey and Baskerville's Anesthesia, 1914, Appleton.

5. We wish to thank Professor Baskerville and Squibb & Sons for their kindness in furnishing the ether used in these experiments.

6. Araki: Ztschr. f. physiol. Chem., 1891-2, xvi, 453.

cent. of sugar. Two tests on dogs showed urinary sugar percentages of 1 per cent. and 1.5 per cent., respectively. The rabbits were given snow baths ranging in length from one hour forty minutes to two hours twenty minutes. The body temperature was lowered to 27 C. or lower. One of the dogs which was subjected to a snow bath for three hours twenty minutes showed a drop in body temperature to 23 C., whereas the other dog, which was placed in an ice-water bath for fifty minutes showed a minimum temperature of 26 C. The former animal had 1.5 per cent. sugar in its urine; the latter animal voided a urine containing 1 per cent. of sugar. The appearance of the sugar was interpreted as due to incomplete oxidation.

Several years later Lüthje[7] and Embden, Lüthje and Liefman[8] demonstrated that the quantity of sugar present in the urine of dogs subjected to pancreatic diabetes was dependent to a degree on the temperature of the dog's environment. For example, one dog kept in a cold room excreted 47 gm. of sugar, whereas the excretion of this same animal was only 4 gm. when the dog was maintained in a warm environment. Lüthje interpreted his results as indicating that under the influence of a cold environment more sugar was produced in an attempt to maintain body temperature by its oxidation.

Brasch[9] and Minkowski[10] in turn strongly criticized Lüthje's findings and conclusions. Brasch experimented with dogs subjected to phlorhizin diabetes and found that the lowering of body temperature had no influence on the sugar excretion. Minkowski and Allard, working with dogs after pancreas extirpation, also demonstrated that a lowered body temperature had no effect on the sugar output. The findings of Lüthje are interpreted by Brasch and Minkowski as being due to the fact that the pancreas was only partly extirpated. This being the case, under the influence of the lowered temperature some glycogen was changed into sugar and passed into the circulation. Mohr[11] confirmed the findings of Brasch and Minkowski in that he was unable to influence the sugar excretion in pancreatic diabetes by lowering the temperature of the animal's environment.

Glaessner[12] calls attention to observations which indicate that a pronounced cooling of the human body by external means, such as cold water, may produce a transient glycosuria. In nine cases of reduced temperature sugar was present in only four instances in the first fractions of urine subsequently passed.

7. Lüthje: Verhandl. d. Cong. f. inn. Med., 1905, p. 268.
8. Embden, Lüthje and Liefman: Beitr. z. chem. Physiol. u. Path. (Hofmeister's), 1907, x, 265.
9. Brasch: München. med. Wchnschr., 1906, vii, 805.
10. Minkowski: Verhandl. d. Cong. f. inn. Med., 1907, p. 272.
11. Mohr: Ztschr. f. exper. Path., 1907, iv, 910.
12. Glaessner: Wien. klin. Wchnschr., 1906, xix, 920.

An interesting experiment on the influence of cold on the sugar excretion in phlorhizin glycosuria has been made by Lusk.[13] In one experiment an 18 kg. dog after fasting for three days and then being permitted to shiver "in the cold of a north wind" for six hours showed an increase of 8.47 gm. in the dextrose output. Exposure to a cold environment for seven and one-half hours on the following day caused an increase of only 6 gm. in the sugar excretion. In the case of another dog (9 kg.) which had fasted one and one-half days, exposure to cold for six hours produced an increase of 4.44 gm. in the dextrose output, whereas a second exposure of six and three-quarter hours on the following day caused no increase in the sugar excretion.

Lusk concludes that the reduction of body temperature by external means "has no effect on sugar production in the fasting organism, except in so far as body glycogen may be converted into dextrose.

Grube[14] has more recently reported data from a series of observations which indicate that no glycosuria follows the anesthetization of meat-fed dogs by means of ether, provided care is taken to maintain the body temperature approximately normal during the anesthesia period. He reports five experiments on dogs ranging in weight from 3.5 kg. to 8.7 kg. in which sugar excretions ranging from a trace to 7.16 per cent. were obtained. The lowering of body temperature ranged from 2.6 to 4.6 C. Grube then noted that no glycosuria resulted in one experiment in which for some unexplained reason the body temperature of the dog under examination was not lowered under the influence of the ether. Following this he made two or three tests in which the body of the animal was maintained at or above the normal temperature during the period of anesthesia. The temperature was regulated by wrapping the dog in cloths and placing the animal on a specially prepared water-bath. In no case was there any sign of glycosuria in an animal whose body temperature had been maintained near the normal by artificial means.

OUR EXPERIMENTS

Dogs were used as subjects. The animals were fed a diet of meat, lard, graham crackers, bone-ash and water during Experiments 1 to 14 (see Table 1) whereas in Experiments 15 to 24 the animals were fed a "carbohydrate-free" diet (see Table 2). Urine collections were made in fractions as voided for thirty-six hours after each anesthetization. The urines were examined by polariscope before and after fermentation.

Three methods of anesthetization were employed, the period of anesthesia being two hours in each instance. The "cone method" consisted in inserting the dog's nose into a perforated tin cone which contained in its bottom a wad of cotton saturated with ether. The so-called "improved method," devised by

13. Lusk: Am. Jour. Physiol., 1908, xxii, 163.
14. Grube: Arch. f. d. ges. Physiol., 1911, cxxxviii, 601.

us, was accomplished by the use of a special apparatus. This apparatus furnishes the animal with warm ether vapor which is saturated with water vapor and mixed with air. This procedure reduces the loss of heat from the body by warming the vapors which are breathed, and by insuring the saturation of the vapors with water causes a reduction in the heat lost by evaporation from the respiratory organs. The current of compressed air insures an abundance of oxygen. For purposes of experiment cold ether vapor was secured by replacing the warm water of the bath by a freezing mixture of salt and ice.

In order to permit the maintenance of normal body temperature during the progress of anesthesia a so-called "thermos-box" was devised. This box was fitted with sixteen sockets for electric light bulbs, each light being capable of individual manipulation. By this means the body temperature of the animal was easily maintained practically constant even during long periods of anesthesia. Losses by radiation and conduction from the surface of the animal were compensated for by the heat furnished by the "thermos-box."

TABLE 1.—Anesthetization of Dogs Which Were Fed on a Mixed Diet *

Experim't No.	Dog No.	Date	Ether Used	Method of Anesthesia	Range of Body Temperature
1	13	11/19	Dehydrated	I. M. cold †	39.0-33.0
2	12	11/21	Dehydrated	I. M. cold	39.0-35.5
3	13	11/23	Dehydrated	I. M. warm ‡	Constant
4	14	11/24	Dehydrated	I. M. warm	Constant
5	12	11/25	Dehydrated	I. M. warm	Constant
6	14	11/28	Dehydrated	I. M. cold	Constant
7	13	11/27	Common	I. M. warm	Constant
8	12	11/29	Common	I. M. warm	Constant
9	13	11/30	Common	I. M. cold	39.2-34.8
10	12	12/ 2	Common	I. M. cold	39.6-36.2
11	13	12/ 3	Common	Cone	39.3-31.6
12	12	12/ 4	Common	Cone	38.8-29.0
13	13	12/ 5	Common	Cone	39.3-32.1
14	12	12/ 6	Common	Cone	39.8-28.7

* Fehling and fermentation tests on urine negative throughout.
† I. M. cold signifies improved method using cold ether vapor.
‡ I. M. warm signifies improved method using warm ether vapor.

If the data from Experiments 1, 2 and 9 to 14, listed in Column 6 of Table 1, be examined, it will be observed that temperature depressions ranging from 3.4 C. to 11.1 C., were obtained in the course of eight experiments. Even with such pronounced lowerings of body temperature, however, the urine never contained a trace of sugar. It is evident, therefore, that so far as our experimental animals are concerned, the lowering of their body temperature by means of ether inhalation did not produce glycosuria.

The body temperature underwent the most pronounced reduction when the anesthetic was given by the "cone method." This was due principally to the extreme dryness of the inhaled ether vapor.

II.—THE FACTOR OF DIET IN POSTANESTHETIC GLYCOSURIA

If the data contained in the final columns of Tables 1 and 2 be examined it will be observed that every anesthetization listed in Table 2 was accompanied by glycosuria, whereas sugar was never present in the urine after the periods of anesthesia listed in Table 1. The only variable factor in the two sets of anesthetizations was the diet. The same animals were used in each series, the same kinds of ether were employed, the anesthetic was given by the same methods and for the same length of time. Previous to the administration of the ether in Experiments 1 to 14, however, the dogs were fed the usual mixed diet, whereas previous to Experiments 15 to 24 they were fed a carbohydrate-free diet.

TABLE 2.—ANESTHETIZATION OF DOGS WHICH WERE FED ON A CARBOHYDRATE-FREE DIET

Experim't No.	Dog No.	Date	Ether Used	Method of Anesthesia	Range of Body Temperature	Dextrose in Urine gm.
15	13	12/14	Dehydrated	I. M. cold	39.0-36.7	0.53
16	12	12/15	Dehydrated	I. M. warm	Constant	0.39
17	13	12/16	Dehydrated	I. M. warm	Constant	0.19
19	13	12/20	Dehydrated	I. M. warm	Constant	0.45
20	15	12/21	Dehydrated	I. M. warm	Constant	0.53
21	14	12/22	Dehydrated	I. M. warm	Constant	0.65
23	12	12/13	Common	Cone	39.7-35.0	1.44
24	14	12/17	Common	I. M. cold	39.0-32.9	0.38

At the beginning of our tests we were exceedingly surprised at our inability to detect any trace of sugar in the urine of our dogs even after the animals had been under ether for a period of two hours. After conducting fourteen experiments on four different animals, using two different ethers and administering the ether by three different methods and failing in any case to produce any sign of glycosuria we decided to note the influence of the removal of carbohydrate from the diet. The data from the series of tests on the carbohydrate-free diet are given in Table 2. An examination of the final column of that table will show that in every instance the anesthetization of an animal which had been fed a carbohydrate-free diet, resulted in the production of glycosuria. Further work is contemplated in order to determine the minimum carbohydrate ingestion which will prevent the occurrence of postanesthetic glycosuria. The data may have a clinical application.

In order to determine whether lack of oxygen during the ether inhalation could of itself cause glycosuria several experiments were made by various methods of anesthesia. A mixed diet was used in

every instance. By the so-called "improved method" the maximum amount of air was mixed with the ether vapor before inhalation, whereas in the "cone method" the minimum amount of air was allowed to be breathed with the ether vapor. There was no glycosuria in any case, indicating that the lack of oxygen in these cases was not sufficient to cause glycosuria.

III.—"DEHYDRATED" VERSUS COMMON ETHER

The dehydrated ether employed was specially prepared for us by Professor Baskerville, whereas the common ether was the regulation Squibb ether. The opinion having been expressed that the postanesthesia glycosuria and other undesirable features accompanying or following ether inhalation were due not to the ether per se, but to some impurity in the ether, we were very glad of the opportunity of making a series of tests in an attempt to elucidate this problem. The particular thing in view in this instance was to determine the relationship of these two types of ether to the ether glycosuria.

In Table 1 are listed six experiments with "dehydrated" ether and eight experiments with common ether. *In no case was glycosuria observed.* The animals were fed a mixed diet. In Table 2 are listed six experiments with "dehydrated" ether and two with common ether. *Glycosuria was observed in each instance.* The dogs were fed a carbohydrate-free diet.

The experiments force us to the conclusion that the glycosuria following ether inhalation is not due to impurities present in the ether, since the purest ether obtainable yields just as pronounced glycosuria as does the regulation Squibb ether used for anesthesia purposes. Our experiments indicate that the occurrence or non-occurrence of glycosuria hinges on the character of the diet, the ingestion of a carbohydrate-free diet yielding glycosuria, whereas the ingestion of a mixed diet is unaccompanied by glycosuria.

CONCLUSIONS

1. The reduction of body temperature during ether anesthesia does not of itself cause glycosuria.

2. The reduction to a minimum of the oxygen content of the ether vapor inhaled does not cause glycosuria.

3. The response of the animal body to "dehydrated" ether (that is, ether from which aldehyd and other impurities have been removed) in so far as glycosuria is concerned, is no different from the response to the ether ordinarily used (Squibb) as an anesthetic.

4. The inhalation of ether administered by the cone method causes a more pronounced reduction in body temperature than does the inha-

lation of the same kind of ether for a similar period when administered by the so-called improved method. The dryness of the ether vapor in the cone method is the contributing factor.

5. The inhalation of either "dehydrated" or common ether for a period of two hours by dogs fed a carbohydrate-free diet was in every instance accompanied by glycosuria. When the same animals were fed a mixed diet glycosuria was not in evidence.

6. There was no evidence of "emotional" glycosuria, the factor regulating the occurrence or non-occurrence of glycosuria in every instance being a dietary one.

We wish to express our thanks to Dr. Paul E. Howe for assistance rendered.

THE COMPLEMENT-DEVIATION TEST WITH BESREDKA'S TUBERCULIN AND THE OCCURRENCE OF TUBERCULOSIS AMONG SYPHILITICS AS DIAGNOSED BY THIS TEST*

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Although tuberculosis is one of the most common of infectious diseases, it is one of the most difficult to diagnose in its early stages. Very many cases progress to spontaneous recovery without ever giving the slightest possibility of diagnosing the process, and only the statistics of post-mortem examinations show how frequently healed and unhealed undiagnosed tuberculous conditions have existed. It is true that by means of the von Pirquet test many cases in which tuberculosis has existed some time during the patient's life can be diagnosed, but the extreme sensitiveness of this test makes it impossible to differentiate cases in the active stages of the disease from those in which the process of the disease was arrested. For this reason the results of the von Pirquet test, though valuable for the exclusion of tuberculosis, are of little value for the diagnosis of the disease, especially in adults. Many and continuous attempts have been made to apply the methods of diagnosis of other infectious diseases to that of tuberculosis, but all of these attempts have so far met only limited success.

In the present communication I shall report on a method of complement deviation in tuberculosis which seems to answer the requirements both of early diagnosis and of differentiation of active tuberculosis from that in which the pathologic condition has apparently been arrested. The main reason why complement deviation in tuberculosis has failed so far, in spite of the many attempts, seems to have been the lack of a suitable antigen. This gap seems at last to have been filled through the discovery by Besredka of a new method of cultivating tubercle bacilli.[1] These organisms, grown on a medium consisting of a suitable mixture of bouillon, egg-yolk and egg-white, show biologic properties distinctly different from those observed heretofore, one of the most striking being the rapidity of their growth,

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1. Besredka, A.: Compt. Rend. Acad. d. Sc., 1913, clvi, 1633.

which equals that of streptococcus, for instance. This culture, heated and deprived of its cellular elements by filtration, proved, in preliminary experiments of Besredka and Manoukhine,[2] to be very efficient both as tuberculin and as antigen for the complement-deviation test.

Professor Besredka's kindness in sending me his antigen, enabled me to substantiate fully his preliminary findings as to the efficiency of his antigen for early diagnosis of tuberculosis, both in animals and in man. Experimental animals (rabbits and guinea-pigs) infected with tuberculosis gave a positive reaction by this method often as early as from seven to ten days after the infection; on the other hand, among a group of six hundred cases examined up to April by this method, I found in many instances this reaction present before any other definite symptoms of the disease were noted.

The technic used in the examination was the following:

Antihuman hemolytic serum was used, with a very small amount of complement, two units, carefully controlled by titration, two units of antihuman amboceptor and 0.04 c.c. of the antigen (tuberculin of Besredka), a quantity which was found to contain more than five antigenic units, being at the same time at least five times smaller than the dose fixing complement by itself. In about the first fifty cases both active and inactive serum was used, showing no difference in the results except for a few specimens which, as they came several days after collection, had developed anticomplementary properties. As, on the one hand, in these cases, heating of the serums was essential for the destruction of the anticomplementary properties, and, on the other hand, it was important to treat all serums alike to obtain comparable results, a uniform technic was adopted, namely, to heat all the serums for half an hour at from 54 c.c. to 56 c.c., using 0.1 c.c. of the serum.[3]

As the antigen used in these experiments is represented by a filtrate of cultures of tubercle bacilli grown on mediums consisting of bouillon, egg-yolk and egg-white, the possibility of non-specific lipotropic fixation had to be excluded. As a control, therefore, a test with a pure lipoid antigen was made in each case. From the very beginning unexpected results were obtained, namely, a great number of the serums giving positive tuberculous reaction by this method, gave also positive Wassermann reaction. Therefore, though Besredka

2. Besredka and Manoukhine: Compt. Rend. Soc. Biol., 1914, lxxvi, 180.

3. Dovidowitch reports (Deutsch. med. Wchnschr., 1914, No. 1, p. 21) that tuberculous serums giving positive reaction with the tuberculin used by him as antigen, failed to fix the complement after being heated for half an hour at 56 C. (132.8 F.), from which he concluded that tuberculous antibody is markedly thermolabile. I found (1909) that fresh serum at times contains substances possessing the power of fixing the complement in presence of antigen containing protein (proteotropic fixation) and that these substances are destroyed through incubation at 56 C. for half an hour. The statement of Dovidowitch suggests, therefore, that the fixation with his tuberculin was of the nature of a proteotropic reaction, and hence his findings. Using Besredka's antigen, serums heated at 56 C. for half an hour continued to fix complement.

in placing his antigen at my disposal suggested to me to study in the main, if possible, the occurrence of the reaction on a series of patients at different stages of their disease, these findings called my attention for the time being to the question of the specificity of this reaction, and I shall in this paper report the results of my findings along these lines.

My work was along two distinct lines. In one series of experiments I tried to prove the independent coexistence of the two antibodies in the same specimen of serum directly, in another series I tried to experiment on patients or animals, as the case might be, and in this way follow the fate of the corresponding reactions.

The first explanation for the coincidence of the positive tuberculous and Wassermann reactions naturally was that serums which had a high lipotropic coefficient fixed also with tuberculous antigen on account of the lipoid it contains. I therefore decided to study the quantitative relationship between the fixing power of the same serums in presence of each of the two antigens. The comparison was made in the following manner:

Each serum was diluted with salt solution, and for each case a series of tubes was set up, in which decreasing amounts of diluted serum were used, the rest of the reagents remaining as above; in this way the minimal dose of serum capable of fixing two units of complement in presence of five units of tuberculous antigen was determined for each specimen of the serum. At the same time, in a parallel series, the same serums were titrated against syphilitic antigen in the same manner, except that instead of the five units of tuberculous antigen five units of pure lipoid antigen were used. Table 1 represents the comparative results of the examination of a few specimens selected out of our series.

Table 1 shows that although a serum may have a high antibody-index as tested against one antigen, it may at the same time show but a very low index against the second antigen, or indeed an index zero, as in Cases 182 or 219 in Table 1, in which Serum 182, for instance, showing 70 units of tuberculous antibody for each 0.1 c.c. showed no antibody at all when tested against syphilitic antigen, proving that there is no relationship between the degree of fixation displayed by the given serum against each of the two antigens. The absence of any regularity in this relationship is especially clearly shown in Table 2. Out of the series of cases I selected 20 giving the same antibody index, as tested against Besredka's tuberculin, as can be seen from Table 2.

These twenty cases gave most varied lipotropic indices; namely, two cases showed quite a high antibody content of 500 units; three cases of 300; two of 150; two of 50; two of 30; one of 10 units and eight cases contained no lipotropic antibody at all. Similarly in other twenty cases with the same lipotropic index, varying tuberculous indices were found, thus illustrating quite conclusively that the rela-

TABLE 1.—Antibody Index with Various Antigens

	Case No.	Amount of Serum Used for Titration (in c.c.)																		Minimum fixing dose in c.c. (unit of antibody)	No. antibody units per 0.1 c.c. of serum
		0.1	0.07	0.05	0.03	0.02	0.015	0.01	0.007	0.005	0.003	0.002	0.0015	0.001	0.0007	0.0005	0.0003	0.0002	0.00015	0.0001		
Examined with 0.0001 c.c. of pure lipoid antigen and 0.03 c.c. of complement.	116	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	MchH	CH	....	....	....	....	....	....	0.002	50
	124	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	....	....	....	0.003	30
	134	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	MchH	CH	....	....	....	....	NoH	FCH	CH	0.0002	300
	154	CH	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	.....	0
	160	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	SlH	CH	....	....	....	....	....	....	....	....	....	0.01	10
	182	CH	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	.....	0
	206	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	CH	CH	....	0.0003	300
	219	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	CH	CH	0.0002	500
Examined with 0.04 c.c. of tuberculin-Besredka and 0.03 c.c. of complement.	116	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	trH	CH	....	....	....	....	....	....	....	....	0.004	25
	124	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	trH	CH	....	....	....	....	....	....	....	0.003	30
	134	NoH	NoH	NoH	NoH	NoH	NoH	NoH	MchH	CH	....	....	....	....	....	....	....	....	....	....	0.01	10
	154	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	SlH	CH	....	....	0.0005	200
	160	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	FCH	CH	....	....	0.0005	200
	182	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	S1H	CH	....	....	....	....	....	0.0015	70
	206	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	MchH	CH	....	0.0003	300
	219	CH	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	.....	0

NoH = No hemolysis or complete fixation (95 to 100 per cent.).
trH = Traces of hemolysis or incomplete fixation (80 to 90 per cent.).
SlH = Slight hemolysis or slight fixation (60 to 70 per cent.).
MchH = Much hemolysis or weak fixation (30 to 50 per cent.).
FCH = Fairly complete hemolysis or very weak fixation (15 to 30 per cent.).
CH = Complete hemolysis or no fixation (less than 15 per cent.).

The numbers in the last column to the right on this table represent the number of antibody units in each 0.1 c.c. of the serum (antibody index). The next column to the left shows the smallest amount of the serum necessary to fix the complement, in other words, the absolute quantity of serum containing one antibody unit for the given serum. By dividing 0.1 c.c. by this number, one can calculate the number of antibody units per 0.1 c.c. of each serum, or its antibody index.

tion between the two antibodies in the same serums does not show any tendency to conform to any law.

In order to decide further whether the two antibodies coexist in the same serum independently, I tried to exhaust one of the presumably coexisting antibodies in the serum by repeated incubation with one of the antigens and subsequently attempted to see whether or not in the process of exhaustion the antibody fixing the complement with the other antigen was removed. The technic of the experiment is the following:

A series of tubes is prepared containing all the ingredients as for routine examination, namely, 0.1 c.c. of heated serum known to give positive reaction with both antigens, 5 fixing units of antigen, plus 2 units of complement, plus 2 units of amboceptor, and salt solution to complete to 1 c.c. The tubes are incubated in water-bath at 37 C. for half an hour. At the end of this time, one tube is taken out from the series and 0.1 c.c. of 10 per cent. washed human blood-corpuscles added, the remaining tubes being kept at room temperature.

TABLE 2.—Showing Variation in Degree of Fixation with Different Antigens

	Tuberculosis Reaction	Wassermann Reaction						
No. of units of antibody..	500	0	10	30	50	150	300	500
No. of cases.....	20	8	1	2	2	2	3	2
	Wassermann Reaction	Tuberculosis Reaction						
No. of units of antibody..	500	0	15	50	100	300	500	More than 500
No. of cases.....	20	6	1	3	3	2	3	2

At the end of half an hour, when in the tube to which the blood-corpuscles were added no hemolysis is observed, all the remaining tubes of the series receive 2 additional units of complement, and 5 additional units of antigen, and are incubated at 37 C. for half an hour. Again one tube is taken out and 0.1 c.c. of 10 per cent. washed human blood-corpuscles added and the tube incubated for half an hour at 37 C., the rest of the tubes remaining at room temperature. If still no hemolysis in the separate tube is observed, the process is repeated, that is, 2 units of complement and 5 units of antigen are added to each tube of the series, one tube of the series tested, etc., until finally all the antibody from the serum is exhausted and the tube in which the test is made shows complete hemolysis. At this point one of the remaining tubes of the series receives 2 additional units of complement, and 5 additional units of antigen, and another tube receives, as before, 2 units of complement and 5 units of the first antigen as a control. After incubation in a water-bath at 37 C. for half an hour, 0.1 c.c. of 10 per cent. human blood-corpuscles are added; and, whereas, in the tube to which the second antigen was added there was no hemolysis, the other shows complete hemolysis, proving that the first antibody is completely exhausted without exhaustion of the second. The technic was slightly simplified in the later experiments and is shown in its simpler form in Table 3. Part "A" of this table should be noted as one hour ahead of Part "B" and in this way the results of "A" show when the exhaustion in "B" should stop.

The experiments shown in Table 3 were also reversed, namely, serum was exhausted of its tuberculous antibody and subsequently the presence of syphilitic antibody was determined. As can be seen from Table 3, the proper controls were carried to show that the fixation after the exhaustion of one antibody and addition of the second antigen was not due to a summing up of fixation by different ingredients, as Serum 280 was tested in absolutely the same manner as Serum 297, yet the addition of tuberculin after the exhaustion of syphilitic antibody in the first case did not cause any fixation, and the fixation in Case 297 therefore should be attributed to the specific antibody present in this serum. The same is true for the two other controls, 285 and 315, treated in a similar way, of which only one, namely 285, fixed complement with the tuberculin on account of the specific antibody it contained.

Although the serologic studies above reported and especially the exhaustion experiment demonstrate quite convincingly that when present in the same serums, the Wassermann reaction and the tuberculin reaction may be absolutely independent of each other, yet, in practice, the coexistence of the two antibodies would have to be proved in each case, as long as the antigen used in the reaction contains lipoid. It was for this reason that I undertook to free the tuberculin of Besredka of its lipoid, in order to eliminate the very possibility of non-specific reaction.[4] The antigen for this purpose was shaken up with ether, chloroform, benzol (benzene), and petroleum-ether in a separating funnel, and, subsequently, the solvent carrying the lipoid was separated from the protein part of the antigen. The latter part alone was then used as antigen for the complement-deviation test. The detailed report of these experiments will be published later in the collaboration with Dr. Rockman, who is comparing the antigenic value of this purified antigen with the original preparation in a number of cases. I may say, however, anticipating this report, that it follows from the 200 examinations up to date, that the value of the antigen was not in the slightest degree diminished by the extraction of the lipoid. As to the lipoid extracted from Besredka's tuberculin, as I expected, it can cause fixation of complement with syphilitic serums, if used in adequate amount: when a large amount of this lipoid, extracted from tuberculin, was collected, the ethereal extract evaporated to dryness, and a very concentrated emulsion in physiologic salt solution (0.03 per cent.) was prepared, it showed undoubted antigenic properties, as would lipoids extracted from any source. It was found, however, that the quantity of this lipoid present in the dose of tuberculin (0.04

4. Bronfenbrenner, J.: Proc. Soc. Exper. Biol. and Med., 1914, xi, 92.

c.c.) used as antigen in the test for diagnosis of tuberculosis, is entirely too small to cause lipotropic reaction, as is evident from the following experiment:

Ethereal extract of the lipoid from 10 c.c. of tuberculin was separated from the aqueous part by means of a separating funnel, concentrated to dryness, taken up with about 0.5 c.c. of ether, and salt solution added to bring the volume back to 10 c.c. In this way the lipoid was brought back to its original concentration in the tuberculin. The resulting emulsion was used as antigen for a Wassermann reaction in the dose (0.04 c.c.) in which the whole tuberculin was used as antigen (using serums known to give a strong Wassermann reaction when tested with 5 units of regular antigen).

TABLE 3.—Results of Experiment to Determine—

A. M.	Number of Exhaustions	Serum 297 0.05 c.c.					
		W (200)			Tb (200)		
9:00	1	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd
9:30	2	Amb Corp	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd
10:00	3	NoH	Amb Corp	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd
10:30	4	....	NoH	Amb Corp	Cpl Lpd	Cpl Lpd	Cpl Lpd
11:00	5	....	....	NoH	Amb Corp	Cpl Lpd	Cpl Lpd
11:30	6	....	....	....	CH	....	....
12:00	..	....	....	....	....	....	....
12:30	..	....	....	....	....	....	....

The number in parenthesis after the sign W and Tb means the titer of the serum with The sign W(0) therefore means Wassermann negative and Tb(0) tuberculous reaction (Cpl) it was throughout this experiment 0.03 c.c.; in case of lipoid antigen (Lpd) it case of amboceptor (Amb) and human corpuscles (Corp) the sensitized corpuscles manner, that each dose of each of the ingredients was represented in 0.05 c.c. volume. The

As can be seen from Table 4, three serums were selected for this experiment, each of them of a high lipotropic index. As to the fixation with Besredka's tuberculin, these serums showed respectively the titers 300, 10 and 0. Now if the fixation with Besredka's tuberculin in the case of Serums 206 and 134 was due to the presence of lipoid in the tuberculin, the emulsion of the lipoid taken in the amount in which it occurs in the tuberculin should, on the one hand, have fixed

the complement with these serums; on the other hand, also Serum 219, showing the property to fix the complement in presence of the lipoid to the same degree (see section "A" Table 4), should have also given a positive reaction with tuberculin (containing lipoid) as well as with the emulsion of pure lipoid, extracted from it. As section "C" in Table 4 shows, no fixation whatsoever took place with any of these serums, however, when the lipoid extracted from the tuberculin was used in the quantity in which it occurs in the tuberculin. Only when the dose of this emulsion of lipoid was increased ten times

—Whether Two Antibodies Coexist in the Same Serum

Number of of Exhaustions	Serum 297 0.05 c.c.		Serum 280 0.05 c.c.		Serum 285 0.05 c.c.		Serum 315 0.05 c.c.		A. M.
	W (200)	Tb (200)	W (200)	Tb (0)	W (0)	Tb (70)	W (0)	Tb (0)	
	....	....	....	....	....	....	....	....	9:00
	....	....	....	....	....	....	....	....	9:30
1	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	10:00
2	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	10:30
3	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	Cpl Lpd	11:00
4	Cpl Lpd	Cpl Tbc	Cpl Lpd	Cpl Tbc	Cpl Lpd	Cpl Tbc	Cpl Lpd	Cpl Tbc	11:30
	Amb Corp	Amb Corp	Amb Corp	Amb Corp	Amb Corp	Amb Corp	Amb Corp	Amb Corp	12:00
	CH	NoH	CH	CH	CH	NoH	CH	CH	12:30

respective antigens; W = Wassermann or lipoid antigen and Tb = tuberculous antigen. negative. The dose of reagents was not indicated on the table. In case of complement was throughout 0.0001 c.c.; in case of tuberculin (Tbc) it was throughout 0.04 c.c.; in carrying amboceptor were used. The amount of the ingredients was arranged in such a total volume in each tube was made up to 2 c.c. before the final incubation.

(see section "D" of Table 4) it began to fix the complement in presence of the largest amounts of the serums. But even there the fixation of the complement is evidently due, not to the specific combination between lipoid serum and complement, but to a summing up of partial complement fixations caused by the large doses of serum as well as by the lipoid emulsion alone,[5] as in case of specific fixation, inhibition of

5. This emulsion of lipoid was anticomplementary in the dose 0.6 c.c.

TABLE 4.—Results of Experiments with Lipoids Extracted from the Tuberculin

		Amount of Serum Used for Titration															
		Case No.	0.1	0.05	0.02	0.01	0.007	0.005	0.003	0.002	0.0015	0.001	0.0007	0.0005	0.0003	0.0002	0.00015
A	0.0001 c.c. of pure lipoid and 0.03 c.c. of compl.	134	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	
		206	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH		
		219	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	
B	0.04 c.c. of Besredka's tuberculin and 0.03 c.c. of compl.	134	NoH	NoH	NoH	NoH	.....										
		206	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH	NoH		
		219	CH	.....													
C	0.04 c.c. of the lipoid from the tuberculin and 0.03 c.c. of compl.	134	CH	.....													
		206	CH	.....													
		219	CH	.....													
D	0.4 c.c. of the lipoid from the tuberculin and 0.03 c.c. of compl.	134	NoH	NoH	CH												
		206	SlH	CH													
		219	NoH	NoH	SlH	CH											

hemolysis should have taken place also with the smaller amounts of serum. In short, although the tuberculin contains lipoid, the amount of the latter contained in the dose of tuberculin used in the test as antigen, is too small to cause any lipotropic reaction with the syphilitic serums. Therefore, the syphilitic serums fixing complement in presence of tuberculin must also contain a tuberculous antibody as was proved in my former experiments.

Although the previous experiments proved quite convincingly the independent coexistence of the two antibodies in the same human serums, I thought the reproduction of this condition experimentally would supply a further interesting proof of the specificity of the fixation with the tuberculin. For this purpose I selected from a series of rabbits having experimental syphilitic orchitis those animals which gave a positive Wassermann reaction. These animals were also tested against Besredka's tuberculin and gave invariably negative results. A series of five normal rabbits was used as a control. As shown in Table 5, Rabbits 102, 105, 109, 111 and 117 gave positive Wassermann at the time of the experiment; Rabbit 118, although likewise infected, developed Wassermann reaction somewhat later. March 5, seven rabbits having experimental orchitis as well as three control rabbits were infected with tuberculosis, and March 15, all of them showed a positive reaction when tested against Besredka's tuberculin by the complement-deviation method. As can be seen from Table 5, three syphilitic rabbits, not infected with tuberculosis, as well as two normal controls, gave at the same time a negative tuberculin reaction. March 17, some of the rabbits, as shown in the table, received, intravenously salvarsan (0.04 gm. per kilogram) which injection was repeated March 21, and the animals were again tested by the complement-deviation method March 30. The animals that had received salvarsan lost their Wassermann reaction, but continued to give positive reaction with Besredka's antigen.[6]

An analogous experiment was performed also on a number of patients who came to the hospital for the treatment of syphilis, and who in addition presented positive serum reaction with Besredka's antigen. Of these cases, there were eight in whom tuberculosis was clinically suspected and in four out of these it was definitely diagnosed. In the remaining four, however, there was no clinical evidence of active tuberculosis though their von Pirquet test was positive. All these cases, as well as control cases presenting the Wassermann reaction only, were repeatedly examined during their treatment, and,

6. The weakening of the Wassermann reaction, March 30, in the Rabbits 100 and 117 (which did not receive any salvarsan), is due to spontaneous cure. They entirely lost their Wassermann reaction when tested April 10.

TABLE 5.—Showing Positive Reaction with Besredka's Antigen After Salvarsan Had Produced a Negative Wassermann

		Rabbits with Experimental Orchitis							Normal Rabbits (Controls)				
Rabbits No.		100	102	105	109	111	117	118	130	131	132	133	134
3/3	W. R. Tb. R.	+ —	+ —	+ —	+ —	+ —	+ —	— —	— —	— —	— —	— —	— —
3/5		Not	infect	ed	In	fected tuber	with culosis		Not in	fected	In tu	fected bercu	with losis
3/15	W. R. Tb. R.	+ —	+ —	+ —	+ <+	+ +	+ <+	«+ «+	— —	— —	— +	— <+	— «+
3/17-21		No salv.	Salvar intra	san ven.	Salva intra	rsan ven.	No sal	varsan	Salv. intraven.	No sal-varsan	No salv.	Salvar intra	san ven.
3/30	W. R. Tb. R.	<+ —	— —	— —	— +	— +	«+ <+	<+ <+	— —	— —	— +	— +	— «+

The sign + means positive reaction.
The sign <+ means weakly positive reaction.
The sign «+ means almost negative reaction.
The sign — means completely negative reaction.

whereas the Wassermann reaction disappeared after a certain period of time in at least fifteen cases, the tuberculosis reaction persisted.[7]

Having thus proved that, on the one hand, the positive reaction with tuberculin is not of a lipotropic nature, and that, when present in serums giving also positive Wassermann reaction, it may be shown to exist separately; and, on the other hand, having caused Wassermann reaction to disappear under treatment from the serums of the experimental animals and human beings giving both reactions without the disappearance of the tuberculosis reaction, I was convinced that complement fixation with Besredka's antigen indicates an independent tuberculous infection whether primary or secondary to other conditions.

These findings are to a great extent borne out also by clinical observations on over 600 cases comprising such widely varying pathologic conditions as typhoid, specific meningitis, tuberculosis, pernicious anemia, cancer, pneumonia, scarlet fever, diphtheria, syphilis, gonorrhea, trichinosis, and various surgical conditions, which were studied up to date. As the majority of cases included in this series was not selected especially but was taken at random as admitted to this hospital, the number of tuberculous patients among them was comparatively small. Through the kindness of Drs. Park, McNeil and Pease of New York I was enabled, however, to bring the total number of cases of known tuberculosis up to 174.[8] On account of the remarkably high percentage of positive tuberculosis reactions found among syphilitics from the beginning of this work,[9] I decided to subdivide all the cases, tuberculous as well as non-tuberculous, according to the positive or negative history of syphilis.

As can be seen from Table 6, among sixty-five cases of active tuberculosis the reaction was present in sixty-one; in the remaining four it was negative. Three out of these four cases were of tuberculous peritonitis (one of them terminating fatally) and in the other two the diagnosis was confirmed by Dr. Andrews from the examination of tissue removed at operation. The fourth case was that of a man in a far-advanced stage of lung tuberculosis with a very great

7. I noticed in two cases some change in the strength of the tuberculous reaction under the influence of salvarsan treatment. Whether this change is due to the effect of salvarsan on tuberculous processes, or whether salvarsan may exert direct influence on the serum reaction, is a question studied at present in my laboratory. I wish to express here my indebtedness to Drs. Schildecker and Walker, who kindly offered their cases for the study of the effect of salvarsan treatment upon the deviation test with the tuberculin.

8. This number comprised cases of active tuberculosis mostly. There were, however, among these twenty-seven cases in which, although there was a very definite history of tuberculosis, no active symptoms had been present for a number of years.

9. Bronfenbrenner, J.: Proc. Soc. Exper. Biol. and Med., 1914, xi, 92.

number of tubercle bacilli in the sputum. Among the 27 cases which were clinically cured or on the way to recovery, 15 gave positive and 12 (44.5 per cent.) negative reaction. It is interesting to notice that among 108 cases of syphilis in which tuberculosis was or was not clinically suspected, there were 41 cases (38 per cent.) with positive reactions. Of the 18 cases showing positive reaction in which tuberculosis was originally not suspected, but syphilis was definitely diagnosed, in 3 cases tubercle bacilli have since been found in the sputum and in 2 others clinical proofs of tuberculosis were present on subsequent rigid examination by Dr. Boyce. It is needless to mention that,

TABLE 6.—Reactions in Tuberculous and Non-Tuberculous Syphilitic Cases

		Tb. R. +	Tb. R.—	Total	Percentage +
No syphilis suspected. Tuberculosis diagnosed or suspected.	Active tuberculosis at present	61	4	65	93.84
	Definite history of tuberculosis, but no symptoms at present (convalescents)	15	12	27	55.5
	Tuberculosis strongly suspected, but not diagnosed definitely	36	14	50	72.0
	Tuberculosis diagnosed or suspected; also syphilis treated and untreated	23	9	32	37.96
	Syphilis treated and untreated. Tuberculosis not suspected	18	58	76	
No syphilis nor tuberculosis suspected.	Different pathologic conditions	6	69	75	8.0
	Controls: surgical, obstetric, gynecologic	18	202	220	
	Controls: cases without any history at the time of serum test; accidents	6	74	80	
	Total	183	442	625	

in the 15 cases of this series on whom the von Pirquet test was made, it was always positive. Out of 75 cases comprising different pathologic conditions except syphilis, in which tuberculosis was not suspected, 6 gave a positive reaction. In 2 cases, which came later to necropsy, Dr. V. L. Andrews found ample confirmation of the serologic diagnosis. Out of 220 cases comprising obstetrical, surgical and gynecological material in which neither tuberculosis nor syphilis was suspected, 18 gave positive reaction. Among these, 5 were in children under 5, with positive von Pirquet; in the remaining 13 cases it was impossible to find confirmation of the serologic diagnosis, because the patients left the hospital very soon after the blood examination was

made. The same applies to the six positive reactions out of the 30 cases in which no history whatsoever was at hand at the time of the serum test. Thus from the material on hand it follows that, except for four cases in extremely advanced stages, the reaction was positive in all the cases of active tuberculosis; that the reaction was negative in about 90 per cent. of cases in which tuberculosis was not suspected, and that, as to the remaining 10 per cent. in which the serum findings were the first to call the attention to the possible presence of active tuberculosis, and in which subsequent clinical or pathologic examination was possible, a confirmation of the serum diagnosis was obtained in many cases though not in all. It is in these latter cases that I tried my serum skin-test, which in every case corroborated the previous serologic findings.[10]

Inasmuch as twelve apparently cured patients with tuberculosis, having given a negative serum-reaction, all continued giving a positive von Pirquet I thought it would be of interest to compare the two reactions.[11] The numbers in Table 7 represent the results of such a comparison on a series of 70 cases.[12]

As can be seen from this table, the von Pirquet test was negative in only nineteen cases and these consisted chiefly of children, twelve

10. Though the number of cases to which this test has so far been applied by me is too small to claim for it unquestionable value, yet the results obtained are sufficiently constant to consider it as additional proof of tuberculosis with other evidences pointing in the same direction. The technic of this test is the following: Fresh serum from the suspected patient is mixed with tuberculin of Besredka in relation 10:1, and 0.05 c.c. of this mixture is injected into the skin of a normal guinea-pig, after the mixture is allowed to stand at room temperature for three hours. Two or three hours after the injection — in case the serum used was tuberculous — the guinea-pig presents thermic reaction, and at the end of twenty-four (forty-eight) hours a local reaction similar to the tuberculin reaction follows. Each series of guinea-pigs is accompanied by a control guinea-pig receiving intradermally the double dose of tuberculin alone. In addition to this, as a control for the serum, each guinea-pig is injected on the side opposite to that of the test injection with the double amount of the suspected serum alone. The results are taken only in those cases where the controls do not show any reaction. This precaution is necessary because some serums show a tendency to cause a local irritation.

11. Since last February I have been studying on a large series of infants, in collaboration with Dr. Pease, the comparative value of the von Pirquet and complement-deviation test. Though this study is incomplete as yet, it is already apparent that accepting the known diagnostic value of the von Pirquet test on infants, it offers a very favorable control to the serum test, thus adding an additional proof of the specificity of the complement-deviation test with Besredka's antigen.

12. This group of individuals was not selected in any way, but simply represents the cases in which I was permitted to perform a von Pirquet test as a control to the serum test. The number of cases is comparatively small, but I was unable to have the von Pirquet performed on all cases on account of the desire to avoid the unnecessary inconvenience to the patient incidental to this test.

being under 5, five under 15 years and only two, adults. The remainder, mostly adults, gave a positive von Pirquet. The serum test, however, was positive only in 30 of the 70 cases. In 18 of the 21 cases in which the von Pirquet was positive and the complement-deviation test negative, there was no clinical evidence of tuberculosis whatsoever; in the remaining 3 cases, however, the results of von Pirquet coincided with the clinical diagnosis of tuberculosis. One of these cases in which meningeal symptoms were present, proved later, however, not to be of a tuberculous nature, showing thus the correctness of the serologic findings against von Pirquet. The other two cases were cases of very advanced tuberculous peritonitis mentioned before. This comparison adds another very important proof of the value of the complement-deviation test in tuberculosis, especially in its active stages.

Inasmuch as, on the one hand, the complement-deviation test was negative not only in 92 per cent. of the cases in which tuberculosis was not suspected clinically, but even in 45 per cent. of convalescents, and, on the other hand, as the suspicion of this reaction being of a

TABLE 7.—Comparative Results of Serum and Von Pirquet Tests

Von Pirquet + Tb. R. +	Von Pirquet + Tb. R. —	Von Pirquet — Tb. R. +	Von Pirquet — Tb. R. —
30	21	0	19

lipotropic nature had been excluded by the above-described experiments, the high percentage of positive reactions obtained among syphilitics in my series becomes very significant. The percentage of 37.9 of positive tuberculosis reaction among syphilitics (as shown in Table 6) should be, in fact, even higher, as in this table only those cases in which the history of syphilis was given on admission were classed in this group. Assuming, however, that the patients giving positive Wassermann reaction (see Table 8) were syphilitics even when their presence in the hospital was due to other causes, the number of syphilitics in this series of 625 cases is 108 (diagnosed as syphilis) plus 85 (giving positive Wassermann reaction whether or not syphilis was suspected at the admission), or, 193. Out of this number of syphilitics 83 gave positive tuberculin reaction (14 giving negative Wassermann and 69 positive Wassermann reaction) being about 43 per cent.; among these cases, however, tuberculosis was diagnosed or strongly suspected in 55 cases (46 with positive and 9 with negative Wassermann) leaving 28 (83 — 55) cases of syphilis in which tuberculosis was not suspected, or, as the total number of syphilitics in whom tuberculosis was not suspected is 138 (193 — 55), the rate of

positive tuberculosis reaction in syphilitics in whom tuberculosis was not previously suspected is about 20.3 per cent.

For non-syphilitics (taking as non-syphilitics all the persons in whom no history or symptoms of syphilis were found and the Wassermann reaction was negative), the corresponding numbers are the following: Total number is 625 — 108 (diagnosed as syphilitics) — 85 (syphilis not diagnosed, but Wassermann reaction positive) equals 432. Out of this number only 100 gave positive tuberculin reaction, or about 23.15 per cent. Among these, tuberculosis was

TABLE 8.—Reactions in Syphilitic Cases Not Previously Suspected of Being Tuberculous

	TB.+W.+	TB.+W.—	TB.—W.+	TB.—W.—	Total
Tuberculosis diagnosed or strongly suspected. (No syphilis suspected)	32	80	2	28	142
Tuberculosis diagnosed or suspected; also syphilis treated and untreated	14	9	4	5	32
Syphilis treated and untreated. Tuberculosis not suspected	13	5	15	43	76
Different pathologic conditions. No tuberculosis or syphilis suspected.....	2	4	8	61	75
Controls (normal) obstetric, surgical accidents, no syphilis or tuberculosis suspected	6	12	22	180	220
Cases without any history or diagnosis at the time of the serum test	2	4	11	63	80
Total	69	114	62	380	625

diagnosed or strongly suspected in 80 cases, which leaves 20 (100 — 80) cases of positive tuberculin reaction out of 352 (432 — 80 diagnosed tuberculosis) cases comprising various pathologic conditions with the exception of syphilis, and practically normal controls, which makes less than 5.68 per cent.[13]

13. This number probably is still smaller, as among those classed as non-syphilitics there may be a certain number of cases of treated or cured syphilis which on account of the absence of definite symptoms and in view of negative Wassermann do not confess a specific history. I had the opportunity of discovering by means of Noguchi's luetin test at least one such case in my series. After the patient under the weight of the evidence, admitted the infection 18 years before, it was duly transferred into the group of treated syphilitics in my series.

Thus the occurrence of tuberculosis, as estimated by the complement-deviation test, is very much higher among syphilitics than among non-syphilitics, as is shown in Table 9.

SUMMARY

The complement-deviation test with Besredka's antigen is not lipotropic in nature. Whenever present in serums possessing high lipotropic property, it depends on the presence of a separate antibody possessing its own index different from the lipotropic index in the same serum.

Serums possessing similar lipotropic indices may therefore have widely different indices when tested with Besredka's antigen.

TABLE 9.—SHOWING GREATER PERCENTAGE INCIDENCE OF TUBERCULOSIS AMONG SYPHILITICS THAN AMONG NON-SYPHILITICS

	Tuberculosis Reaction Positive with Besredka's Tuberculin				
	Tuberculosis Clinically Diagnosed or Strongly Suspected	Tuberculosis Clinically not Diagnosed nor Suspected	Total Number of Positive Tb. R.	Average Percentage	
				Among All Cases	Among Non-Diagnosed as Tuberculous
193 syphilitics	55	28	83	43.0	20.3
432 non-syphilitics.	80	20	100	23.15	5.68
Total number of 625	135	48	183	29.28	9.79

When the serum deviates the complement in presence of both Besredka's tuberculin and pure lipoid antigen, each of the two antibodies can be exhausted from the serum independently of each other.

Besredka's tuberculin can be freed of its lipoid without losing its antigenic property.

The presence in the same serum of the property to fix complement with both antigens independently can be reproduced in experimental animals, and, when present in human beings (as well as in animals), the lipotropic antibody disappears under salvarsan treatment, whereas the tuberculous antibody persists.

The comparison of the results obtained by the complement-deviation test with those obtained by von Pirquet and their analysis in the

light of the clinical histories of the cases points to the evident specificity of this complement-deviation test.

The findings of other workers who had the opportunity of using Besredka's antigen are even more convincing. Whereas, in my series, the percentage of positive reactions in cases of active tuberculosis was 93.84 per cent, Inman,[14] for instance, reports 95 positive reactions in 100 patients showing tubercle bacilli in the sputum. As to the cases, comparatively few in number, in whom, in spite of active tuberculous processes, the reaction gave negative results, the clinical picture of the cases as well as the data in my possession from the study of this reaction on experimental animals seem to suggest that in the latest stages of the disease the circulating antibodies seem to disappear from the blood.[15]

The question if the antibody is bound by the excess of the free circulating antigen (which seems most probable) is being studied at present in my laboratory by the method of Debré and Paraff.[16]

The high percentage of negative reactions among clinically non-tuberculous (92 per cent.), together with the other proofs of the high degree of specificity of this reaction, seem to indicate that the comparatively frequent simultaneous occurrence of the complement-deviation test with Besredka's antigen and the Wassermann reaction in syphilitics is due to the fact that either syphilis as such or the antisyphilitic treatment markedly lower the resistance of the patients so as to make them either more susceptible to new infection of tuberculosis or to render them less resistant against the progress of this disease previously contracted.

14. Inman, Compt. Rend. Soc. de Biol., 1914, No. 4, p. 251.
15. Bronfenbrenner, J.: Science, 1914, xxxix, 804; Proc. Soc. Exper. Biol. and Med., 1914, xi, 92.
16. Debré and Paraff: Compt. Rend. Soc. de Biol., 1911, July 8, 16, 23, 28.

A CLINICAL STUDY OF TWO HEPATIC FUNCTIONAL TESTS

(GALACTOSE AND PHENOLTETRACHLORPHTHALEIN)*

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The object of this paper is to add further clinical observations to those already assembled on the subject of hepatic function. A voluminous literature has been assembled already on the subject both from an experimental and clinical standpoint. A very excellent general review of this is set forth in Holweg's[1] publication later reviewed and amplified by Riess and Jehn.[2] The more recent work has been presented by Rowntree, Hurwitz and Bloomfield.[3] In this study we have limited ourselves to the use of two tests, namely, the galactose test and the phenoltetrachlorphthalein test. These seemed to offer the greatest possibilities from a clinical point of view.

I. GALACTOSE TEST

The structural formula of d-galactose is $CH_2OH\ (CHOH)_4\ COH$. Its stereo-isomere is dextrose. It can be formed by hydrolysis from lactose. It rotates polarized light to the right. It ferments with greater difficulty than does glucose.

Relatively little experimental work has been carried out with galactose in connection with hepatic function. Sachs[4] showed that if the liver was removed from frogs a decreased tolerance to levulose was produced; however, no change in the tolerance to galactose was observed. Later Kausch and Socin showed that this was not true in dogs. Bauer's[5] later clinical observations confirmed these findings, thus showing that the ability to utilize galactose in men and dogs was different from that in frogs. Kausch and Socin[6] also showed that galactose with dextrose, saccharose, maltose and levulose must be considered as a glycogen-former. Hofmeister[7] showed, however, that the toler-

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1. Hohlweg: Deutsch. Arch. f. klin. Med., 1909, xcvii, 443.
2. Reiss and Jehn: Deutsch. Arch. f. klin. Med., 1912, cviii, 187.
3. Rowntree, Hurwitz and Bloomfield: Bull. Johns Hopkins Hosp., 1913, xxiv, 327.
4. Sachs: Ztschr. f. klin. Med., 1899, xxx, 87.
5. Kausch and Socin: Arch. f. Exper. u. Pharmak., 1893, xxxi, 398.
6. Bauer: Wien. Med. Wchnschr., 1906, vi, 2537.
7. Hofmeister: Arch. f. exper. Path. u. Pharmak., 1889, xxv, 240.

ance in dogs was a great deal lower for galactose than for the other sugars. Of interest is the work of Drauat,[8] who showed that the tolerance to galactose in a dog after an Eck fistula is reduced 79 per cent., while in the case of lactose it is reduced 42 per cent. More recently Fischler[9] has shown that after an Eck fistula in a dog the animal will tolerate the same amount of dextrose and levulose as before the operation; however, 80 per cent. of all ingested galactose appears in the urine. Drauat[8] concludes that the liver has a peculiar function in being able to utilize the galactose as no other organ. He states that a galactosuria would seem to indicate that there is a greater or less shunting off of the normal parenchyma of the liver or at least that the blood does not circulate through it. Roubitschek[10] has shown that, in rabbits with hepatic lesions produced by phosphorus, intolerance to galactose could be demonstrated. Wörner[11] made similar observations showing that the intolerance was in direct proportion to the degree of liver injury and independent of renal irritation. Roubitschek[10] also noted an increase in tolerance as more chronic lesions were produced. Of importance also is the work of Riess and Jehn,[2] in which they conclude from their experiments on dogs that the effect of mechanical obstruction of the common duct (ductus choledochus) per se causes no change in liver function as estimated by the galactose output. From an experimental standpoint, therefore, the use of galactose, as of dextrose and levulose, for a test of hepatic function is based on the power of the liver to change galactose as well as the other monosaccharids, to glycogen. The greater importance of the liver in the utilization of this sugar is a special argument for its use.

Bauer[5] in 1906 first utilized galactose as a clinical means for diagnosing liver diseases. The studies thus far carried out have not given uniform results. The findings of Hirose,[12] Frey[13] and others are of no value for comparative study, as these authors used different amounts of galactose. Of little interest also are the results of Strauss,[14] who made a comparative study of the uses of galactose and levulose. He used a smaller amount of galactose than employed by Bauer.[5] No definite conclusions can be drawn from his findings. Bauer gave his patients 40 gm. of galactose and considered an output above 3 gm. as pathological. He found that 90.6 per cent. of his thirty-two cases of cirrhosis of the liver, 100 per cent. of his forty-three cases of catarrhal

8. Draudt: Arch. f. exper. Path. u. Pharmak., 1913, lxxii, 457.
9. Fischlet: Verhandl. d. Kong. f. inn. Med. in Wiesbaden, 1913.
10. Roubitschek: Deutsch. Arch. f. klin. Med., 1912, cviii, 225.
11. Wörner: Deutsch. Arch. f. klin. Med., 1913, cx, 293.
12. Hirose: Deutsch. med. Wchnschr., 1912, xxxviii, 1414.
13. Frey: Ztschr. f. klin. Med., 1911, lxxii, 383.
14. Strauss: Deutsch. med. Wchnschr., 1913, xxxix, 1780.

jaundice and 8.3 per cent. of sixty cases of localized conditions in the liver gave an abnormal output. Bondi and König,[15] using the same amount of galactose, found that 100 per cent. of eight cases of catarrhal jaundice put out more than 3 gm. Riess and Jehn[2] also gave 40 gm., but considered an output of 2 gm. as pathological. These authors found that 33.3 per cent. of fifteen cases of cirrhosis, 88 per cent. of seventeen cases of catarrhal jaundice, 25 per cent. of eight cases of cholelithiasis and 40 per cent. of five cases of icterus syphiliticus gave abnormal outputs. All of the five cases with tumors of the liver gave normal outputs. (Four of these were confirmed by autopsy.) Lattin[16] also, considering an output of 2 gm. as pathological, found that 10.5 per cent. of nineteen normals, 29 per cent. of seven cases of cirrhosis, 66 per cent. of three cases of catarrhal jaundice showed an abnormal amount in the urine. (It should be stated that one of these catarrhal jaundice patients was given the galactose late in the disease.) All of Lattin's eight patients with chronic passive congestion excreted less than 2 gm.

It is evident from the results of previous investigations that no far-reaching conclusions can be drawn. All authors seem to agree that a marked galactosuria in hepatic disease indicates the presence of a so-called catarrhal jaundice. Further clinical studies must be carried out before the value of the test under other conditions can be established.

The technic employed in this study has been similar to that advocated by Bauer.[17] Forty gm. of galactose are given by mouth at 6 a. m. in 200 or 300 c.c. of tea. The usual breakfast is given one hour later. The urine is collected for a period of six hours after the ingestion of the galactose at two-hour intervals. This urine is tested for sugar. The following tests have been employed: Fehling's, Nylander's and in some cases the fermentation test. The amount of sugar is estimated with the polariscope. The saccharimeter used for glucose determinations is employed. The specific rotation of galactose, according to Lippman, is 80.6 degrees, that of glucose 52.8 degrees. It is therefore necessary to divide the galactose readings by 1.4 as the rotation of galactose is this much greater than that of glucose. The chemically pure galactose (Merck) has been used. An output of above 2 gm. has been considered pathological.

In this study the cases have been classified according to the clinical picture as follows: (1) normal cases (Table 1); (2) cases of icterus catarrhalis; this group may include cases of cirrhosis of the liver with

15. Bondi and König: Wien. med. Wchnschr., 1910, ix, 2617.
16. Lattin: Post-Graduate, 1913, xxviii, 368.
17. Bauer: Deutsch. med. Wchnschr., 1908, xxxviii, 1505.

jaundice due possibly to a superimposed condition not unlike that of icterus catarrhalis (Table 2); (3) cases of cirrhosis of the liver without jaundice (Table 3); (4) cases with occlusion of the common or cystic ducts of long standing (Table 4); (5) miscellaneous hepatic conditions (Table 5). Twenty-nine cases have been studied.

Little study has been made of the output of galactose in normal individuals. The results, based largely on negative findings and previous observations, show that in the majority of cases less than 1 gm. is excreted.

Four cases of icterus catarrhalis have been studied (Table 2). Seventy-five per cent. of these showed a very definite abnormal output. Case 10 was given the test during the late stages of the disease.

Eleven cases of cirrhosis of the liver have been studied (Table 3). Accurate determinations were impossible in one case, as the patient vomited after taking the galactose. Ten per cent. of the ten remaining showed an increased output. None of these patients were febrile or showed any evidence of jaundice. Fifty per cent. of them had very marked ascites, but showed results similar to those without ascites. Case 25 is of interest, as it represents clinically a very typical case of cirrhosis and hemachromatosis, but had a normal tolerance to galactose. Case 16 was controlled by autopsy and a very characteristic diffuse atrophic cirrhosis found. The diagnosis in Case 23 was confirmed at operation. With two exceptions this series of cases has been observed for several months and there is very little doubt clinically concerning the diagnosis.

Six cases with jaundice showing complete biliary stasis extending over a long period of time were given the test (Table 4). At the time of entrance some of these cases presented the diagnostic problem of the existence of a catarrhal jaundice. None of these cases showed an abnormal output. Necropsies were performed on Cases 29 and 32 and the diagnoses confirmed. In the case of No. 32, a cirrhosis of the liver and metastatic tumor nodules in the liver were found on histological examination. Notwithstanding this the galactose tolerance was normal.

In Group 5 (Table 5, miscellaneous cases) is the one case of exophthalmic goiter (Case 35). The output in this case was 2.5 gm.

Thirty determinations of galactose output have been made on the twenty-nine patients. The nausea and vomiting so common after the ingestion of the necessary amounts of other sugars as levulose are generally absent. We have had but a single case that had diarrhea after the ingestion of the galactose. The administration of a Dover's powder has been found entirely unnecessary. This has been advocated by some authors to combat a diarrhea that might be elicited and thus

insure better absorption. This procedure adds an unnecessary complication. The technic of the test, together with the determinations of the sugar in the urine, is so simple as to require no further discussion. The estimation of the blood-sugar after the ingestion of the galactose has been suggested as a more accurate method to determine the hepatic function.

From the foregoing observations and from previous studies it seemed justifiable to assume that patients with icterus catarrhalis have an intolerance to galactose. On the basis of this fact we are led to consider this condition one primarily involving the bile capillaries within the parenchyma of the liver and not a condition due primarily to obstruction of the pars intestinalis of the common duct. In favor of this view is the fact that experimental ligation of the duct or occlusion of the duct by tumors does not cause a change in the sugar tolerance. Also this conception is further supported by the observations of Bauer, in which he showed gradual return to the normal tolerance as the condition improved. There is little evidence in support of the idea that cases of cirrhosis of the liver show a galactosuria after 40 gm. of galactose. The marked discrepancies in the results thus far published are possibly due to incorrect clinical diagnoses, lack of necropsy on the cases, or to different classification of cases. In reviewing the protocols of the cases previously reported it will be seen that many patients are said to have had marked jaundice. In many cases this may be due to a superimposed process not unlike that found in icterus catarrhalis. This later condition might well be considered to be a precursor of a cirrhosis. Some of the cases of cirrhosis of the liver with a low tolerance to galactose may also be associated with changes in the glands of internal secretion, as exophthalmic goiter, or with certain so-called neurasthenic conditions. These later conditions often show a galactosuria, as shown by the studies of Hirose.

II. PHENOLTETRACHLORPHTHALEIN TEST

The second test applied in this study is the phenoltetrachlorphthalein test. This compound was first prepared by Orndoff and Black.[18] Later it was studied by Abel and Rowntree.[19] These authors established its pharmacological properties with special reference to its action as a cholagogue. They noted that when given subcutaneously the drug escaped from the body only in the bile. It was on this property that its use as an hepatic test was based. Of interest pharmacologically and as a test are the very low toxicity of the dye and the fact that it is excreted in the bile in twenty minutes after the injection, and reabsorbed only to a slight extent by the large intestine.

18. Orndoff and Black: Am. Chem. Jour., 1909, xii, 349.
19. Abel and Rowntree: Jour. Pharmac. and Exp. Therap., 1909, I, 233.

Whipple, Mason and Peightal,[20] and Whipple, Peightal and Clark[21] working on dogs, established experimentally the value of phenoltetrachlorphthalein as a means to determine hepatic function. These authors found in the normal feces the output is from 40 to 50 per cent. They produced hepatic lesions by the use of chloroform and phosphorus and found that following this a definite diminution of the output of the dye resulted. They state that "the drop in phthalein output appears to run parallel to the amount of parenchymatous injury." Of interest in this connection is the gradual increase in output as regenerative changes take place. In view of the work of Whipple aand Hurwitz[22] it is conceivable that after regenerative changes take place periods of hypersecretion follow.

In the light of the foregoing experimental findings, Rowntree, Hurwitz and Bloomfield[3] applied the phenoltetrachlorphthalein clinically as a test for hepatic function. These authors administered the dye as an aqueous solution of the disodium salt. Eighty determinations were made on sixty-seven patients. No very definite conclusions were drawn. These observers believe, however, that the normal output may vary from 30 to 52 per cent. Pyrexia apparently has no effect per se on the liver function. Secondary anemia must be extreme before the excretion of the dye is decreased. The liver function as indicated by this test becomes seriously affected only in those cases in which myocardial insufficiency is extreme.

We have followed essentially the technic as suggested by Rowntree.* The drug has been prepared fresh every two or three days. Four hundred mg., equal to 8 c.c. of the solution, have been given in 100 c.c. of normal saline. The normal saline solution has been used to avoid any hemolytic action such as had been recorded by Krumbhaar.[23] Before giving the dye, great care has been taken to insure excellent catharsis. Magnesium sulphate, from 15 to 20 gm. was given in the morning at 6, the injection at about 12; this was followed by 1 or 2 compound cathartic pills at intervals, depending on the result. Little attention thus far has been paid to the diet. It is my impression that patients on liquid diet do not make collections as satisfactorily as those on the regular "house" diet. The dye is given intravenously with a gravity apparatus. The stools are collected for the next forty-eight hours. As a matter of fact, we have found that there is practically never any further excretion after thirty-six hours. It is not unlikely

20. Whipple, Mason and Peightal: Bull. Johns Hopkins Hosp., 1913, xxiv, 207.
21. Whipple, Peightal and Clark: Bull. Johns Hopkins Hosp., 1913, xxiv, 343.
22. Whipple and Hurwitz: Jour. Exper. Med., 1911, xiii, 136.
23. Krumbhaar: Jour. Am. Med. Assn., 1914, lxii, 992.

*We are indebted to Dr. L. G. Rowntree for the phenoltetrachlorphthalein used in these studies.

that the test could be carried out satisfactorily in a period of twenty-four hours. The personnel of the ward is carefully instructed concerning the collection. On some occasions transfer of excreta from one container to another has caused low outputs due to the loss of feces left in the first container. The precautions taken for careful collections cannot be overemphasized. With this in view the test has been carefully demonstrated to pupil nurses. The stools are tested separately for the presence of phenoltetrachlorphthalein by adding a drop of alkali to a few drops of the diluted feces. If the specimen turns to a pink or reddish color it is saved. The total excreta amount on an average to from 1,000 to 1,500 c.c. Exact dilution to either amount is made; this is shaken thoroughly for about five minutes, depending somewhat on the consistency of the specimens. If a shaker is not at hand the shaking may be satisfactorily done by placing the excreta in a 2-liter bottle and shaking it manually. One-tenth of this amount is now taken, and to this is added about 5 c.c. of a 40 per cent. solution of sodium hydroxid. This amount is by no means fixed. Sufficient alkali is added to insure a maximum intensity of color. As the reaction of specimens varies, the amount of alkali varies. The maximum color can be easily determined by taking small portions in test-tubes and adding alkali until the maximum color appears. An excess of alkali causes a pinkish shade. The aforesaid amount of feces is now diluted to 1,000 c.c. It is shaken for two or three minutes. One hundred c.c. of this are now taken and a saturated solution of basic lead acetate added, 5 c.c. being usually the correct amount. We have found that it is safe to add until no further precipitation of the bile pigments occurs. As pointed out by Whipple, the lead acetate often lowers the reading 2 or 3 per cent. A few cubic centimeters, usually about 5, of 40 per cent. sodium hydroxid are now added until the maximum color is established. Here again great care must be taken not to add an excess of alkali. Small amounts are taken in test-tubes and tested out at various degrees of alkalinity until the maximum color is obtained. The solution is diluted to 200 c.c., filtered and read in the Rowntree-Geraghty modification of the Autenrieth-Königsberger colorimeter. The percentage is read by making up a standard solution as follows: 0.4 c.c. of the original solution of tetrachlorphthalein are diluted to 1,000 c.c. after the addition of a few drops of 40 per cent. sodium hydroxid. We have always used a standard made from the same solution as used for injection. We have experienced little difficulty in obtaining a color that can be read accurately. We have found that the readings are more satisfactory if artificial illumination is used.

After injection of the dye we have observed but one definite reaction. This was in Case 27. The patient was convalescing from an

operation and the exact cause of the fever (101 C.) after the injection is not definite. In five cases we have noted local thrombi at the site of injection. These have had no relation to the disease of the patient and have caused very little discomfort. The same condition is often observed after the injection of salvarsan.

In the selection of cases we have endeavored as far as possible to employ such as present the question of some hepatic disease as a definite or very possible diagnosis. A division of cases similar to that in the galactose studies has been made. Where possible, the same patient has been given both tests. The dye has been given fifty times to 39 patients. Owing to faulty collections, the results of tests made on only thirty-three cases have been reported.

On studying Table 1 it will be seen that seven patients have been selected who unequivocally were not suffering clinically from any hepatic disease. These showed an output ranging from 30 to 44 per cent. A number of other patients, later shown not to be suffering from any hepatic disease, gave similar results. Case 5 later came to necropsy and showed normal hepatic findings histologically. This patient had an output of 32 per cent.

The cases of icterus catarrhalis (Table 2) and those showing complete biliary stasis of long standing (Table 4) are not adapted for study of hepatic function by means of this test. (The recognition of the biliary obstruction should be made by the determination of bile in the urine and in the blood.) It is self-evident that incomplete as well as complete biliary obstruction invalidates the results of the test.

Case 9 (Table 2) is of some interest. It shows the steady increase in output of the dye from a period of total biliary obstruction. At a period, however, when there was no evidence of the catarrhal jaundice clinically, when there was no evidence of bile in the blood or urine, the output continued low. A temporary injury to the liver cells undoubtedly persisted after the obstruction had disappeared. This is quite in harmony with our interpretation of the disease from studies with the galactose test.

Eleven cases of cirrhosis of the liver (Group 3) have been studied. None of these cases showed any evidence of biliary stasis. Five, or 49 per cent. of the total number of cases, showed a distinctly low output. One case (No. 16) in which the collections were excellent and the output was 19 per cent., was carefully controlled by autopsy findings. A typical atrophic "hobnail" liver was found. Histologically, this showed a very diffuse atrophic type of cirrhosis, there being great irregularity in the size of the lobules and no marked evidence of regenerative changes. The remaining five cases in this group showed a normal to relative high output.

Of interest from a prognostic standpoint is Case 28 among the group with biliary stasis. This case was considered to have a tumor involving the head of the pancreas with a question of metastasis in the liver. A cholocystduodenostomy was done. A few days later the phthalein output was practically normal, showing that there were not extensive lesions in the liver. This was actually the case clinically. The patient was seen thee months later; he had gained 10 kg. in weight, and his jaundice had totally disappeared. In this case the test also gave an easy method to determine the presence of bile in stools that contain blood. A few cubic centimeters of the dye are injected intravenously and the feces collected. From these the bile and blood pigments are removed by precipitation with lead acetate and filtration, and the filtrate is made alkaline with sodium hydroxid. The presence of the color due to the dye indicates that bile has entered the intestine.

The cases in Group 5 (miscellaneous) show such varied conditions clinically that a discussion of the results is hardly warranted. Cases 33 and 40 show results similar to Rowntree's two cases of neoplasm involving the liver. Unfortunately, the diagnosis in our cases was not controlled by operation.

The results of the studies with phenoltetrachlorphthalein show, as Rowntree pointed out, that the normal output of the dye in the feces is about 35 per cent. The inapplicability of the test to cases with evidence of biliary stasis makes its scope limited. In the light of the results obtained in cases of cirrhosis it must be borne in mind that many cases are associated with periods of regeneration of liver cells and at times might well be expected to show a normal or increased function. The experimental work of Whipple is in harmony with this conception.

CONCLUSIONS

1. The galactose test may be of great value in differentiating icterus catarrhalis from other hepatic conditions showing biliary stasis.

2. The galactose test is rarely positive in cases of cirrhosis of the liver showing no evidence of biliary stasis.

3. There is no apparent relation between the excretion of galactose and phenoltetrachlorphthalein.

Further studies must be undertaken before any definite conclusions can be drawn concerning the use of phenoltetrachlorphthalein as a hepatic functional test.

Judging from the experimental studies and from the clinical observations noted up to this time, it would seem that a more exhaustive application of the test is justified. It offers a means of diagnosing certain cases of cirrhosis of the liver and of neoplasms of this organ. The results obtained may also be of some prognostic value.

PROTOCOLS

CASE 1.—Diagnosis: Chronic cardiac disease; mitral stenosis.

This patient's history essentially negative except for an attack of rheumatic fever at 9. His present complaints, shortness of breath and precordial pain.

His heart was found to be enlarged; there were signs of mitral stenosis and auricular fibrillation. The abdominal and liver findings were not remarkable; there was no edema. Except for a tonsillectomy his condition was uneventful. He was discharged after forty-three days, improved.

Clinical Pathology: Findings essentially negative.

Phenoltetrachlorphthalein, 44 per cent.

Note: Test given when patient was up about ward with no subjective symptoms.

CASE 2.—Diagnosis: Arteriosclerosis; myocarditis; angina pectoris.

This patient had no alcoholic history and had always been in excellent health. He came to the hospital because of attacks of precordial pain, pain in shoulders and dyspnea.

His heart enlarged to the left; there were no murmurs; except for general arteriosclerosis his physical examination not important. His liver not enlarged. The abdominal findings not remarkable.

Clinical Pathology: Blood: findings normal. Wassermann blood reaction negative. Stool: findings normal. Urine: findings normal.

Phenolsulphonephthalein, 60 per cent. in two hours. Phenoltetrachlorphthalein, 40 per cent.

Note: After the dye was given patient vomited repeatedly. In my opinion there were definite gastric symptoms before the injection and these were accentuated by the catharsis.

CASE 3.—Diagnosis: (Syphilis of aorta) aortitis syphilitica; chronic myocarditis.

This patient had no alcoholic history. Previous to his present illness he had fourteen attacks of cardiac decompensation, there was marked dyspnea, cough and orthopnea. He came to the hospital with these symptoms.

His physical examination at the time the test was performed showed no signs of cardiac decompensation, his heart was enlarged, he had a dilated aortic arch. His liver was not enlarged; he had no edema. He was up about the ward.

Clinical Pathology: Findings essentially negative except for a positive Wassermann (blood). The renal tests showed normal findings.

Phenoltetrachlorphthalein, 41 per cent.

CASE 4.—Diagnosis: Carcinoma of breast.

Nine years ago this patient had a radical operation for a scirrhous carcinoma of her left breast. Eight years later she noted a lump in this region. She had no subjective symptoms.

Except for the small nodules over the site of the previous operation the physical findings negative.

Clinical Pathology: Findings normal.

Phenoltetrachlorphthalein, 32 per cent. (in feces).

CASE 5.—Diagnosis: Aortitis; aneurysm of thoracic aorta.

Patient's family history unimportant. He had exanthems in childhood; also pneumonia one year ago. He had nocturia, subject to dizzy spells, drank about two "whiskies" a day. He came to the hospital because of a gnawing pain in lower abdomen of ten weeks' duration. He vomited a few times. The pain had been fairly constant. Patient lost about 25 pounds during the past year.

Physical examination showed a rather poorly nourished, pale man. There was slight tenderness in epigastric region; an indefinite mass felt. The liver not enlarged. There was no evidence of fluid in the abdomen. Patient died

suddenly; ruptured aneurysm was found at necropsy. The microscopic hepatic findings were negative.

Clinical Pathology: Findings unimportant except for positive Wassermann. Phenoltetrachlorphthalein, 32 per cent. Galactose, no grams.

Case 6.—Diagnosis: Fibromas with pigmentation (von Recklinghausen's disease).

This patient had always enjoyed excellent health. He made very poor progress in school. He came to the hospital because of symptoms referable to hyperchlorhydria.

He showed numerous congenital defects beside the presence of numerous nodules over the body.

Clinical Pathology: Findings normal.

Phenoltetrachlorphthalein, 34 per cent.

Case 7.—Diagnosis: Pleurisy, chronic.

This patient used alcohol in great excess. Except for an attack of pleurisy eight years ago his history unimportant. He came to the hospital complaining of a cough and pain in the right side.

Physical examination showed signs of a fibrinous pleurisy over the right lower lobe. His course was afebrile; entirely uneventful.

Clinical Pathology: Urine showed a small trace of albumin and many white blood-cells. Phenolsulphonephthalein test, 59 per cent. output in two hours. Stool and blood showed essentially negative findings. Phenoltetrachlorphthalein, 36 per cent.

Case 8.—Diagnosis: Disseminated sclerosis.

This patient's personal and past histories unimportant. His gait became progressively more unsteady for the past three years, the ataxia was so marked that he became practically helpless.

The case was typical of multiple sclerosis, with intention tremor, nystagmus, scanning speech, exaggerated knee-jerks, ankle-clonus and Babinski. There was no sensory involvement.

Clinical Pathology: Findings normal.

Galactose excreted, 1.19 gm.

Case 9.—Diagnosis: Catarrhal jaundice.

Complaint: "Pain in stomach and yellowness." Six weeks ago he had intermittent dull, well localized epigastric pain, accentuated by stooping forward. His sleep had not been interrupted. His pain had no relation to meals. About five weeks ago he began to vomit, generally about half an hour after meals. This continued up to one week ago. Vomitus contained no blood. Patient did not think it contained bile. His appetite remained good, his bowels regular. One week ago his eyes and skin became yellow, his stools clay-colored. His urine had been dark-colored for three or four weeks.

He was a well-nourished and developed young man. His skin light yellow in color, also the sclera. The abdomen showed no areas of tenderness, no muscle spasm. The liver dulness extended from the fifth rib to 1 cm. below the costal margin in the nipple line. The edge felt 3 cm. below the costal margin in the right nipple line. Patient's course in the hospital was entirely uneventful. He had practically no subjective symptoms. He was observed about four weeks and discharged well.

Clinical Pathology: Urine contained bile until shortly before discharge. Urobilinogen was increased. Stools on entrance were clay-colored (contained bile at time of last test). Galactose, 2.6 gm., given at admission.

Phenoltetrachlorphthalein: Feces, 0; urine, 6 per cent., two days after admission; feces, 10 per cent.; urine, 0, ten days after admission; feces, 20 per cent.; urine, 0, three weeks after admission.

Case 10.—Diagnosis: Cirrhosis of liver; catarrhal jaundice.

This patient had been an habitual drinker. He had always been a remarkably healthy individual. He came to the hospital because of swelling of his

legs. There had been some epigastric discomfort of late; otherwise no subjective symptoms.

His skin and sclera yellow-tinged; the liver markedly enlarged. There was possibly free fluid in the abdomen. There was edema and also a purpuric discoloration of the legs. After about two months the jaundice practically disappeared. In six months, however, patient came to the hospital again. This time he was much more jaundiced. His liver was still very much enlarged. His condition on both admissions was febrile for a number of weeks.

Clinical Pathology: Renal tests normal. Urine contained a slight trace of albumin and much bile during his last admission. Urobilinogen much increased. Blood: normal findings. Wassermann blood reaction negative. Stool often light-colored and evidently contained reduced amount of bile.

Galactose, first admission, 0.18 gm.; second admission, 1.7 gm.

Phenoltetrachlorphthalein test (second admission), trace in feces.

CASE 11.—Diagnosis: Jaundice, catarrhal; cirrhosis of liver (?)

There was a *definite alcoholic history*. Patient used malt liquors, gin and wine, apparently often in excess. Her general health had always been good. She had never been seriously ill, been jaundiced or had any previous gastric symptoms. Five weeks before admission patient had a smothering sensation about the heart; about two weeks later had an attack of nausea and vomiting. Simultaneously the sclerae became yellow. The vomiting persisted up to admission, she had no abdominal pain.

On physical examination the skin was lemon yellow in color; the sclera also yellow. There was apparently moderate enlargement of the liver; otherwise the findings negative. Patient was observed about three weeks, her jaundice and vomiting cleared up in that time.

Clinical Pathology: Urine: bile present. Urobilinogen increased. Feces: bile present. Wassermann positive. Blood: findings negative.

Galactose, 4.3 gm.

CASE 12.—Diagnosis: Catarrhal jaundice.

The patient's past and personal histories unimportant. About six weeks before admission she began to vomit; this persisted up to the time of admission. She had been nauseated and complained of epigastric pain almost constantly. She had not been jaundiced.

Her physical examination showed a slightly enlarged heart. The abdominal findings normal. The liver not enlarged. Her stay in the hospital was uneventful.

Clinical Pathology: Urine amber-colored, a slight trace of albumin; bile present. Stools contained no bile and were clay-colored on certain examinations.

Phenoltetrachlorphthalein output, 10 per cent. (feces clay-colored).

Note: Patient's stay in the hospital was so short that repeated tests could not be made.

CASE 13.—Diagnosis: Cirrhosis of liver (?); catarrhal jaundice.

This patient had always been in excellent health. He had had no previous illness; there was no alcoholic history. For the past three months patient said he had had indigestion, complained of eructation of gas, of a gnawing sensation in the epigastrium, some nausea and persistent vomiting for the past thirty-six hours. His skin had been yellow for the past two weeks.

On physical examination one noted icterus of the skin and sclerae. Save for marked enlargement of the liver, the abdominal findings were negative. The edge of the liver sharp, the surface smooth. Patient's course in the hospital was entirely uneventful, his jaundice disappeared, he had no subjective symptoms after one week.

Clinical Pathology: Urine: bile present, large amounts of urobilinogen. Blood shows normal findings.

Galactose, 3.9 gm.

CASE 14.—Diagnosis: Cirrhosis of liver; chronic nephritis (?).

This patient had an alcoholic history. About two years ago she first became dyspneic on exertion. Associated with this were edema of the feet, nycturia and polyuria. Her abdomen had been distended for the past year. She had had constant nausea for the past two weeks, some headache.

Her facies markedly alcoholic, her heart moderately enlarged; her blood-pressure 180 systolic, diastolic 95. She was obese. Her abdomen showed no signs of free fluid; the upper border of the liver began at the level of the fifth rib and extended 10.5 cm. below the costal margin in the right nipple line. The edge smooth, rounded. Patient's condition improved subjectively while in the hospital.

Clinical Pathology: Renal test, phthalein 60 per cent. in two hours. Urinary findings normal.

Galactose, 0 gm. Phenoltetrachlorphthalein, first test (feces), 22 per cent.; second test (feces), 21 per cent.

CASE 15.—Diagnosis: Nephritis, chronic; cirrhosis of liver.

Patient had no previous illness of note. He always used alcohol, two or three glasses of whisky and two or three glasses of beer a day. For the past year he complained of swellings of his legs. He noticed swelling of his abdomen for the past six months; associated with this there had been moderate dyspnea. Patient markedly emaciated. There was marked edema of the ankles, legs, scrotum and sacral region. There were signs of fluid in the abdominal and pleural cavities (verified by repeated paracenteses). There was some cardiac enlargement; a slight hypertension. He was observed about four months. Tappings, limitation of fluids, Karell diet, diuretin, theocin, digitalis and sweat baths gave no relief.

Clinical Pathology: Phenolsulphonephthalein from 40 to 52 per cent. in two hours (repeated tests). No nitrogen retention. Slight sodium chlorid retention. Normal outputs of sodium iodid and lactose. A normal specific gravity of urine, always a trace of albumin with many hyaline and granular casts. Ascitic fluid: characteristics of a transudate.

Liver tests: Galactose after 40 gm.; 0.4 gm. excreted. First phenoltetrachlorphthalein, 22 per cent. recovered; second, 20 per cent. recovered.

CASE 16.—Diagnosis: Cirrhosis of the liver.

Patient came in with complaint of "tightness" in the abdomen, especially on the right side. This was of four months' duration. He was constipated; he had no other subjective symptoms; however, he had not worked since the onset of his illness.

Physical examination showed a moderately well-nourished and developed Chinaman. There was no evidence of jaundice. There were signs of fluid in the pleural cavity, marked ascites. Of note was the enlargement of the superficial veins extending from the axilla down. The liver edge could not be felt, before or after tapping.

Abdominal paracentesis was performed on twelve different occasions. About 5 or 6 liters of fluid recovered each time; had the characteristics of a transudate. Inoculation of guinea-pigs with the fluid gave negative results.

Microscopic examination of liver taken from operation showed typical lesion of a diffuse atrophic cirrhosis.

Clinical Pathology: Wassermann reaction of blood, urinary findings, kidney function tests, stool examination and blood examination gave negative findings except for a high (108) urobilinogen content in the urine.

Phenoltetrachlorphthalein, 7 per cent. (poor collections.) Second phenoltetrachlorphthalein, 19 per cent. (excellent collections). Galactose 0.9 gm.

CASE 17.—Diagnosis: Cirrhosis of liver.

Since the age of 20 patient drank three or four glasses of beer and one or two of whisky a day. More recently he drank ten or twelve whiskies a day with additional beer. He had measles and two attacks of pneumonia, but his general health had been good. He came into the hospital complaining of swell-

ing of the legs, dizziness, dyspnea on exertion, a dull pain in the lower abdomen. He vomited very often in the morning; marked anorexia.

His face was deep red; there was dilatation of the superficial veins of the face. There was no jaundice. His abdomen was prominent; on admission there were signs of fluid in the abdomen; this was not verified later by paracentesis. His liver extended from the fifth intercostal space to 10 cm. below the costal margin. Palpation of the edge disclosed nothing remarkable. The superficial veins over the left abdominal half are prominent; there is edema of the ankles.

The patient remained in the hospital nineteen days; was discharged greatly improved, with no evidence of abdominal fluid, no edema.

Clinical Pathology: Wassermann negative. Urine: high specific gravity, no bile, albumin, small trace; occasional granular cast. Urobilinogen ten times normal amount. Feces and blood normal.

Liver: Phthalein, 40 per cent. recovered in feces. Galactose, 0.4 gm.

CASE 18.—Diagnosis: Nephritis, chronic. Cirrhosis of liver (?).

This patient used liquor in great excess. He had typhoid fever; his general health good. He came to the hospital complaining of headache and vomiting. He had no dyspnea. Moderate nycturia.

Physical examination essentially negative. He had a hypertension — 190 systolic, and slight enlargement of the liver.

Patient's stay in the hospital was uneventful.

Clinical Pathology: Renal test, phenolsulphonephthalein from 30 to 42 per cent. in two hours (repeated). Urine showed a trace of albumin, many hyaline casts, rare red blood-cells, no bile. Blood: findings normal.

Phenoltetrachlorphthalein, first test, feces 19 per cent.; second test, 25 per cent.

CASE 19.—Diagnosis: Nephritis, chronic; cirrhosis of liver (?); frontal sinusitis.

Patient's history is markedly alcoholic, 1 quart of whisky a day; three "whiskies" before breakfast. "Dry heaves" every morning. He had been working in a brewery for the past seven years, had no previous illness except measles. He complained of headaches, swelling of the ankles, face and hands, vomiting, had three hemoptyses. There had been moderate dyspnea.

Physical examination showed an enlarged heart, a slight hypertension. Liver enlarged; the upper border at the level of the upper border of the sixth rib in the right nipple line, the edge 4.5 cm. below the costal margin, no edema, no icterus.

After about three weeks' stay in the hospital his subjective symptoms disappeared; his physical examination remained unchanged.

Clinical Pathology: Urine showed a trace of albumin and many hyaline and granular casts; no bile. Phenolsulphonephthalein test showed 45 per cent. excretion in two hours. Blood: findings normal.

Liver tests: Galactose, 0.7 gm. Phenoltetrachlorphthalein, 20 per cent. (collections excellent).

CASE 20.—Diagnosis: Cirrhosis of the liver; catarrhal jaundice.

There was a marked alcoholic history, seven or eight glasses of whisky a day. Patient had no definite history of any previous illness. About three weeks before entrance his eyes became yellow. He spat blood on a few occasions; had marked malaise, no other subjective symptoms.

His skin and sclera were icteroid in color. His liver began 3 cm. below right nipple and extended 5 cm. below costal margin in right nipple line. The edge hard and regular. No evidence of fluid in the abdomen. His stay in the hospital was uneventful. His icterus entirely disappeared.

Clinical Pathology: Wassermann negative. Urine: no bile. Blood normal. Stool normal.

Galactose, 0.94 gm.

Case 21.—Diagnosis: Cirrhosis of the liver.

Patient always been in excellent general health. He had been a moderate user of alcohol, one or two glasses of whisky, three or four glasses of beer a day. He had measles, scarlet fever and small-pox as a child. He had "indigestion" for the past five years. He had heartburn, eructations, etc., without gastric pain, vomiting or hematemesis. There had been moderate edema of the ankles for five years, also constipation with hemorrhoids. There had been no jaundice. For the past five weeks patient's abdomen increased in size, until there were such marked distention that he experienced considerable shortness of breath.

On physical examination a fairly well-developed and nourished man. There was no abnormal pigmentation of the skin. He had moderate cardiac enlargement, a systolic blood-pressure of 220. His abdomen greatly distended. There were evidences of fluid. The liver not enlarged; the edge easily felt after paracentesis, firm, nodular and rounded. In the region of the epigastrium a firm, rounded, small, hen's egg-sized mass, that moves with inspiration.

Clinical Pathology: Roentgen examination of the stomach gave negative findings. Patient showed a secondary anemia, a negative Wassermann reaction, normal urinary findings, negative findings in stools. The phenolsulphonephthalein output in the urine varied from 21 to 51 per cent. The ascitic fluid was greenish yellow; it contained 0.6 per cent. albumin and 500 cells per cubic millimeter.

Phenoltetrachlorphthalein, 36 per cent.

Case 22.—Diagnosis: Cirrhosis of liver.

This patient had a marked alcoholic history. He drank from six to ten glasses of whisky daily, also additional beer. Except for a history of typhoid fever seven years ago he enjoyed excellent health up to the present illness. For the past four weeks he had recurrent hemoptyses, morning nausea and sour eructations.

On physical examination his heart was found to be very much enlarged (17 cm. to left of midsternal line in the sixth interspace). There was a murmur of mitral insufficiency. The abdomen is protuberant; the superficial veins of the abdomen dilated. There was dulness in the flanks, but no fluid wave demonstrable. The liver dulness extended from the fifth interspace to 8 cm. below the costal margin in the right parasternal line. The edge felt rounded, but smooth. There was no edema of the extremities.

Clinical Pathology: Urine: normal findings; other findings normal.

Phenoltetrachlorphthalein, 46 per cent. Galactose, 2.21 gm.

Case 23.—Diagnosis: Cirrhosis of the liver.

This patient denied the use of alcohol in any form. In September, 1912, patient first noted enlargement of her abdomen. This persisted, and she was tapped thirteen times. She complained of severe pain in the abdomen.

Of importance, on physical examination, were the abdominal findings. There was marked distention, shifting dulness; a fluid wave was made out. The patient was not jaundiced.

Patient was transferred to the surgical service where an Eck fistula was attempted. This was not carried out on account of the presence of hepatic adhesions. The liver was found to be small and retracted upward. Its surface was irregular; had the characteristic "hobnail" appearance. An omentopexy (modified Talma operation) was performed. Patient's condition was unrelieved. She died about two and one-half months after the operation. No necropsy was secured.

Clinical Pathology: Ascitic fluid, specific gravity, 1.012, clear, contained few mononuclear cells, 1.5 per cent. albumin. Urine and blood: findings essentially negative.

Galactose Test: Forty gm., given on two different occasions; gave a slight trace in the urine each time. The test was not satisfactory, however, as on

one occasion patient vomited soon after taking the galactose, on the other occasion there was considerable diarrhea.

Phenoltetrachlorphthalein Test: This was the first test performed and some difficulty was experienced in reading the results. It is safe to say that a relatively high percentage was recovered — 50 per cent.; no dye was found in the urine.

CASE 24.—Diagnosis: Syphilis of the liver (?); cirrhosis of the liver.

This patient's past and personal histories unimportant. She had pain for many years in the upper right abdominal quadrant. About eight months ago her abdomen began to swell and she was tapped repeatedly during the following months. There had been no jaundice, no edema. She lost much weight.

On physical examination the hepatic dulness began at the fourth rib and was continuous with the abdominal dulness. After paracentesis the liver edge was felt 8 cm. below the costal margin in the right nipple line. The patient's condition became progressively worse. Antisyphilitic treatment had been carried out.

Clinical Pathology: Urine: findings normal. Blood: Wassermann positive. Phenoltetrachlorphthalein, 45 per cent.; galactose, 1.4 gm.

CASE 25.—Diagnosis: Hemachromatosis; cirrhosis of the liver.

Patient 68 years of age. Twenty-three years ago he fell injuring his abdomen (the exact nature of the injury not ascertained). Since this time he thought his skin had been very dark. He drank two or three "whiskies" a day for many years. He came into the hospital because of sensation of nausea and general malaise. Also his legs had been swollen.

On physical examination his skin everywhere dark brown in color. It had a definite bronzed appearance. There were purpuric spots over the extremities. His abdomen not distended. His liver edge felt 6 cm. below the costal margin in the midclavicular line. There was a large elevated area over the mass that corresponds to the liver. The liver apparently enlarged. Patient showed evidence of much loss in weight.

Clinical Pathology: Urine: Findings normal. Other findings not important. Section from skin showed presence of pigment (not hemosiderin).

Galactose, 0.6 gm.; phenoltetrachlorphthalein, trace in feces.

CASE 26.—Diagnosis: Cirrhosis of liver.

This patient forty years of age, used liquor in great excess for many years. He always enjoyed excellent health. About three months ago he suddenly became jaundiced; this disappeared in two weeks. Associated with this he had anorexia and pain in epigastrium. Six weeks ago he developed ascites and edema of legs. He had been dyspneic and had attacks of epistaxis.

Of importance on physical examination were the signs of fluid in the pleural and abdominal cavities and edema of legs. He was not jaundiced. There were distended superficial abdominal veins.

Clinical Pathology: Urine: normal findings, no bile. Blood: normal findings. Ascitic fluid, characteristics of a transudate.

Galactose, trace. Phenoltetrachlorphthalein, feces, 36 per cent.; urine, trace.

CASE 27.—Diagnosis: Cholelithiasis (common duct?); carcinoma of head of pancreas.

At times patient used alcohol to excess. He complained of dull epigastric pain, anorexia, frequent attacks of feeling cold and feverish, also of loss of weight and itching of the skin.

The skin and sclera had a marked icteric tint. The liver markedly enlarged. At times a mass corresponding to the gall-bladder had been palpated.

This patient was observed for one year. At times the icterus cleared markedly but recurred. His general condition remained fairly good. He refused operation.

Clinical Pathology: Renal tests normal. Urine always showed a slight amount of albumin and often trace of bile and many granular casts. Stools,

in general clay-colored, at times, however, normal. Blood: evidences of a mild secondary anemia.

No phthalein or galactose recovered.

Case 28.—Diagnosis: Carcinoma of head of pancreas (?).

For the past seventeen years patient used no alcohol. His past history unimportant. About ten weeks before admission he complained of a burning sensation in the epigastrium; three weeks after this time he became yellow; the jaundice persisted. There had been no abdominal pain. On one occasion he was feverish. There had been marked loss of weight and much pruritus.

On physical examination he showed evidence of much loss of weight; his skin is jaundiced, lemon yellow. The sclera were intensely jaundiced. The liver markedly enlarged; a mass corresponding to the gall-bladder palpated. There was no abdominal tenderness. X-ray examination, also proctoscopic examination, showed negative findings.

He was operated on December 30. The condition at operation was thought to be carcinoma of the head of the pancreas. A cholecystenterostomy was performed. Patient made a satisfactory postoperative recovery. Bile again appeared in the stools; the jaundice disappeared to a great extent. The recovery was so remarkable that the original diagnosis seemed questionable.

Clinical Pathology: Urine shows presence of bile. Urobilinogen present in traces. Stool clay-colored; a negative guaiac. Wassermann blood reaction negative.

Galactose, 0 gm. Phthalein none before operation; 29 per cent. after operation.

Case 29.—Diagnosis: Carcinoma of head of pancreas.

This patient, 52 years of age, had vomited persistently for three months, complained of pain in his abdomen, lost weight and been jaundiced for a number of weeks.

Physical examination showed very marked jaundice of the skin and sclerae. A mass felt which extends 2 cm. below the umbilicus; hard, rounded and undoubtedly corresponded to a lobe of the liver. A mass corresponding to a distended gall-bladder was made out.

An exploratory laparotomy was performed. Patient died four days after the operation from hemorrhage. At autopsy a carcinoma of the head of pancreas was found. This had caused compression of the bile-ducts.

Galactose 0 gm.

Case 30.—Diagnosis: Cholelithiasis.

This patient had pertussis, diphtheria and measles in childhood. At the age of 12 she was jaundiced for several weeks. She had malaria twenty-three years ago. She had attacks of severe diarrhea, also attacks of "gastric distress," especially during the past year. On one occasion she had sharp, shooting pain in the right upper abdominal quadrant; this was accompanied by chills, sweats and fever. She became jaundiced in twenty-four hours and has remained so.

On physical examination there was marked icterus of the skin and sclerae. The abdominal findings essentially negative, except for slight tenderness below the umbilicus on the right; liver showed no signs of enlargement.

Patient was afebrile while under observation; she had no subjective symptoms. After two weeks the icterus disappeared. She refused operation.

Clinical Pathology: Urine showed the presence of bile. Urobilinogen was increased. Blood: findings normal. Stools showed no abnormalities.

Galactose, 1.25 gm. Phthalein, 14 per cent.

Case 31.—Diagnosis: Carcinoma of head of pancreas involving common duct.

This patient had always drunk one or two glasses of whisky or one or two "beers" a day. He had had no previous illness. About two weeks before admission he first noted that his urine was highly colored, his stools became

clay-colored and he became jaundiced. These conditions persisted. He experienced slight pain in the region of the crest of the ilium on the right.

His skin was icteroid; he was poorly nourished, the abdomen full, several distended superficial abdominal veins. The liver markedly enlarged, the dulness beginning in the fifth interspace and extending 9.5 cm. below the costal margin in the right parasternal line. The edge rounded, the surface slightly uneven. A mass felt in the region of the gall-bladder.

Patient's stay in the hospital was uneventful; an exploratory laparotomy was advised.

Clinical Pathology: Urine contains much bile. Blood: findings essentially normal. Stools contain no bile.

Galactose, 0.69 gm.

CASE 32.—Diagnosis: Carcinoma of head of the pancreas.

This patient was 52 years of age. He used liquor in excess for a long period of time. Following a fall a few days before admission he complained of pain in lower abdomen and in epigastrium. Simultaneously he became jaundiced.

On physical examination his skin was icteroid, his sclerae yellow. His liver flatness was greatly increased. A tumor was felt in the region of the gall-bladder.

Patient's condition became markedly worse. He developed cholemic symptoms and died four weeks after admission.

Necropsy showed a carcinoma involving the head of the pancreas and duodenum. The bile and pancreatic ducts were greatly distended; the liver was large, showing some cirrhosis and metastatic nodules.

Clinical Pathology: Urine contained much bile. Wassermann reaction was positive. Stool contained no bile. Galactose, 0.17 gm.

CASE 33.—Diagnosis: General carcinomatosis.

This patient was operated on eighteen months ago for "cancer" of the breast. A scirrhous carcinoma was removed. Since the operation she lost much weight, had recurrent epistaxes, marked tinnitus, and malaise.

Patient markedly emaciated and very pale. The superficial lymph-nodes were enlarged; there were questionable areas of consolidation in the lungs. There was abdominal distention, with evidence of fluid in the abdominal cavity, of an enlarged liver, of a massive tumor in the region of the spleen. Patient was observed for two months. The course of the disease was not unlike that of pernicious anemia. X-ray examination showed numerous areas in the skull and long bones suggestive of multiple carcinomata.

Clinical Pathology: Blood, repeated examinations, hemoglobin from 35 to 60 per cent.; red blood-cells 1,020,000. Urine, normal findings. No Bence Jones bodies. Stool, normal findings.

Galactose none. Phenoltetrachlorphthalein, 8 per cent.

CASE 34.—Diagnosis: Cirrhosis of the liver (?); adhesive pericarditis; Pick's syndrome.

When 16 years of age patient had rheumatic fever. He had a recurrent attack twelve months ago. He had not used alcohol in excess. Two years ago he developed dyspnea which became progressively worse. There had been ascites from the onset. He had been tapped repeatedly.

Physical examination showed a poorly nourished man with cardiac enlargement, with evidences of adhesive pericarditis. There were signs of fluid in the abdomen, marked edema of both legs, and evidences of collateral circulation. After paracentesis his liver was found to be enlarged. Patient observed on the wards for two months. Except for repeated abdominal tappings his course was uneventful.

Clinical Pathology: Urine showed normal findings. Phenolsulphonephthalein test: 47 per cent. output in two hours (repeated). Blood: findings not remarkable.

First phenoltetrachlorphthalein, trace; second, 8 per cent. Galactose, 0.2 gm.

CASE 35.—Diagnosis: Exophthalmic goiter.

This patient has always enjoyed excellent health. About one year ago she began to lose weight; her eyes became prominent and her hands unsteady; she perspired freely and complained of palpitation of her heart.

Of note on physical examination were the exophthalmos, the presence of a Von Graefe sign, a marked tremor of the hands, the absence of a struma, a slightly enlarged heart.

The patient had two attacks of tonsillitis while under observation. Later a partial thyroidectomy was performed with relief.

Clinical Pathology: Urinary findings, normal. Blood: a moderate lymphocytosis.

Galactose, 2.5 gm. Phenoltetrachlorphthalein, 30 per cent.

CASE 36.—Diagnosis: Chronic interstitial nephritis.

This patient had frequent attacks of tonsillitis; "dysentery" on three occasions while in the Philippines. Seven months ago his condition was diagnosed as nephritis at the Massachusetts General Hospital. His chief complaints were headache and failing vision. There had been some frequency of micturition and polyuria.

Patient was observed some six months and finally died in uremia. Clinically he represented a classical picture of chronic nephropathy. Blood-pressure 235. Marked albuminuric retinitis.

Clinical Pathology: Urine: specific gravity 1.010. The sediment showed numerous casts and a large trace of albumin. Phenolsulphonephthalein output 20 per cent. in two hours. Feces contained much blood during last few days of life.

The phenoltetrachlorphthalein was given while patient was in uremia. A trace was recovered in the stools.

Necropsy showed a slight degree of central necrosis.

CASE 37.—Diagnosis: Peritonitis (tuberculous).

The previous history of this case unimportant. The patient complained of enlargement of her abdomen.

The physical examination showed a rather poorly nourished woman, abdomen markedly distended, signs of fluid in the abdominal cavity, no signs of collateral circulation.

On three occasions, after abdominal paracentesis, indefinite nodular masses were felt in the epigastric region. The liver was not enlarged. Pelvic examination showed negative findings. Patient was observed three weeks; her course was uneventful. After six weeks she again returned for paracentesis. At this time the masses in the epigastric region were somewhat larger than formerly. She had lost little weight. Patient was under observation about six months. She died at her home; necropsy not performed.

Clinical Pathology: Ascitic fluid: characteristics of an exudate, specific gravity, 1.021; 2.1 per cent. albumin; a lymphocytosis. Guinea-pigs injected with the fluid showed no evidence of tuberculosis. Stool, urine and blood showed normal findings.

Phenoltetrachlorphthalein, 32 per cent.

CASE 38.—Diagnosis: Chronic cardiac valvular disease.

This patient had a severe attack of rheumatic fever at the age of 14. In other particulars her past and personal histories unimportant. She had had cardiac symptoms for the past twelve years and repeated (six or eight) attacks of broken compensation.

Her skin had an icteroid tinge; the sclera were similarly pigmented. The heart was enlarged and there were signs of a mitral stenosis and regurgitation. The blood-pressure was slightly elevated. The abdomen distended but no evidences of fluid. The liver dulness began at the level of the fifth rib and the edge felt 9 cm. below the costal margin in the right mammary line. At times it pulsated; there was edema of the extremities.

Clinical Pathology: Urine contained no bile but a large trace of albumin. The findings were essentially normal otherwise.

Phenoltetrachlorphthalein output, 27 per cent. (test given during period of decompensation).

CASE 39.—Diagnosis: Tuberculosis (chronic, pulmonary); tuberculous peritonitis; nephritis, chronic; amyloid (?); amyloid liver (?).

Patient's past history unimportant. He had been a moderate user of alcohol. Three months ago he began to be dyspneic; he then developed edema of his legs and a slight cough with profuse expectoration.

Physical examination showed definite pulmonary involvement. The abdomen showed evidence of fluid; the liver was not enlarged. There was edema of the extremities.

Patient was under observation thirty-nine days. His course was febrile; he was discharged unimproved. During his stay in the hospital he developed a bloody diarrhea, otherwise his condition was uneventful.

Clinical Pathology: Sputum showed tubercle bacilli. Urine: average of 1.030 specific gravity; always contained a trace of albumin (from 1 to 3 per cent.); many hyaline and granular casts. Phenolsulphonephthalein output in two hours was 50 per cent. Stools contained much blood; no tubercle bacilli. Blood showed normal findings.

Phenoltetrachlorphthalein, 14 per cent.

CASE 40.—Diagnosis: Carcinoma of stomach (?) with metastases; cholelithiasis (?).

This patient had always taken one or two glasses of beer a day, also whisky occasionally. About twenty-six years ago she had gastric symptoms which were ascribed to a gastric ulcer, also occasional attacks of indigestion since, characterized by burning pain in the stomach. For the past nine months patient had severe cramp-like pain originating about the umbilicus and radiating toward the left axilla. She had repeated attacks lasting three or four days, with no jaundice; ten days ago she had a very severe attack, with much vomiting, diarrhea, fever. Following the attack she had marked tenderness over the right hypochrondrium. There had been considerable loss of weight.

The liver was found to be enlarged, tender, with questionable nodules over the lower surface. An indefinite mass made out, apparently connected with the liver, extending to the umbilicus.

Patient was observed twenty-one days; the acute attack subsided. She refused operation. Her general condition was unimproved. X-ray examination showed a typical hour-glass stomach.

Clinical Pathology: Gastric examination showed a marked anacidity. Gastric infiltration and x-ray findings showed an hour-glass pattern. Stool and urine examinations showed nothing abnormal. Wassermann reaction was negative. Blood: negative findings.

First phenoltetrachlorphthalein, 10 per cent.; second, 20 per cent.

CASE 41.—Diagnosis: Tuberculous peritonitis.

This patient's personal history unimportant. He enjoyed excellent health up to two months ago, when his abdomen began to swell. He had been constipated.

On physical examination he was found to be very poorly nourished. There were questionable signs of pulmonary involvement. The abdomen manifested signs of fluid in the peritoneal cavity. After paracentesis the liver was found to extend 7 cm. below the costal margin. It was smooth except for a nodular elevation below the xyphoid process.

Below the angle of the left scapula there was an abscess formation. Pus and tissue recovered from this showed tuberculous lesions. Guinea-pigs injected with it developed tuberculous lesions. Patient's course was febrile; he became progressively worse and died about four months after onset of the disease. Necropsy not obtained.

Clinical Pathology: Otherwise unimportant.

Galactose: 0.6 gm.

TABLE 1.—NORMALS

Case No.*	Hospital No.	Diagnosis	Galactose gm.	Phthalein † Feces (%)	Remarks
1	M. 394	Cardiac chr. valvular	.....	44	Lesion well compensated when test was given.
2	M. 544	Cardiac	.....	40	Lesion well compensated when test was made.
3	M. 460	Cardiac	.....	41	Compensated when test was made.
4	Huntington Hosp.	Carcinoma of breast	.....	32	
5	M. 755	Syphilis	0.0	32	Autopsy.
6	M. 808	Von Recklinghausen dis.	.....	34	
7	M. 818	Pleurisy	.....	36	
8	M. 30	Spastic paraplegia	1.5	..	

*The salient features of each case in this and the following tables will be found in the accompanying protocols.

†None was found in the urine in any case.

TABLE 2.—CATARRHAL JAUNDICE (ICTERUS CATARRHALIS)

Case No.	Hospital No.	Diagnosis	Galactose gm.	Phthalein Per Cent.	Remarks
9	M. 785	Icterus catarrhalis (uncomplicated)	2.6	1— 0 feces 6 urine 2—10 feces 0 urine 3—20 feces 0 urine	Galactose given day of admission. First phthalein two days after admission. Second phthalein ten days after admission. Third phthalein given three weeks after admission.
10	M. 158	Icterus catarrhalis; cirrhosis of liver.	1st—0.18 2d —1.7	† feces † urine	Galactose given on first admission (see history). Second galactose given in later periods of disease. Stools clay-colored at time phthalein was given.
11	M. 423	Icterus catarrhalis; cirrhosis of liver.	4.3	Not given	
12	M. 585	Icterus catarrhalis	Not given	10	Stools clay-colored at time of test.
13	M. 147	Icterus catarrhalis	3.9	0	Jaundice totally disappeared while in hospital.

†Trace.

TABLE 3.—CIRRHOSIS OF LIVER

Case No.	Hospital No.	Diagnosis	Galactose gm.	Phthalein Per Cent.	Remarks
14	M. 757	Cirrhosis	0.0	1—20 feces 0 urine 2—20 feces 0 urine	Excellent collections.
15	M. 316	Cirrhosis, nephritis (chronic)	0.4	1—22 feces 0 urine 2—20 feces 0 urine	Excellent collections.
16	M. 769	Cirrhosis	0.9	1— 7 feces 0 urine 2—19 feces 0 urine	Collections of first phthalein test not satisfactory. Necropsy.
17	M. 442	Cirrhosis	0.4	40 feces † ?	
18	M. 678	Cirrhosis, nephritis (chronic)	*	1—20 feces 0 urine 2—25 feces 0 urine	
19	M. 489	Cirrhosis, nephritis (chronic)	0.7	Test performed. Collections unsatisfactory.	
20	M. 171	Cirrhosis	0.94	.....	This case may also represent a condition of icterus catarrhalis in the last period of the disease.
21	M. 816	Cirrhosis	0.0	1—36 feces 0 urine	Excellent collections.
22	M. 1030	Cirrhosis	2.21	36 feces 0 urine	
23	M. 36	Cirrhosis	‡	45 feces 0 urine	Patient vomited after taking galactose.
24	Huntington Hosp.	Cirrhosis (syphilitic)	1.4	45 feces 0 urine	
25	M. 1151	Haemachromatosis, cirrhosis of liver	0.6	†	
26	M. 1168	Cirrhosis	†	36 feces † urine	

* Not given. ‡ Unsatisfactory. † Trace. † ? Slight trace in urine.

TABLE 4.—Cases with Jaundice Due to Obstruction of Common or Cystic Duct

Case No.	Hospital No.	Diagnosis	Galactose gm.	Phthalein Per Cent.	Remarks
27	M. 5	Cholelithiasis; carcinoma of head of pancreas	0.0	0 feces † urine	At time of test urine contained much bile, the stools were clay-colored.
28	M. 634	Carcinoma of head of pancreas	0.0	1— 0 feces † urine 2— 0 feces 3—29 feces 0 urine	First phthalein test was given before operation, with bile in urine. Second given three days after operation. Third three weeks after operation. Jaundice practically disappeared. Stools normal color.
29	M. 281	Carcinoma of head of pancreas	0.0	.....	Necropsy. Diagnosis confirmed.
30	M. 506	Cholelithiasis	1.25	14 feces 0 urine	Patient was slightly jaundiced at time of test.
31	M. 1028	Carcinoma of head of pancreas.	0.69	.....	
32	M. 310	Carcinoma of head of pancreas; cirrhosis of liver.	0.37	.....	Necropsy. Diagnosis confirmed.

TABLE 5.—Miscellaneous

Case No.	Hospital No.	Diagnosis	Galactose gm.	Phthalein Per Cent.	Remarks
33*	M. 602	Multiple carcinomatosis	0.0	8 feces †? urine	Excellent collections.
34	M. 710	Polyserositis	0.2	1— † feces 0 urine 2— 8 feces 0 urine	Excellent collections.
35	M. 405	Exophthalmic goiter	2.5	30 feces 0 urine	
36	M. 146	Nephritis (chronic); uremia	.....	† feces	Test made when patient was in uremia, two days before death. The catharsis for the first eighteen hours excellent. Much blood in stools.
37	M. 687	Peritonitis (tuberculous)	0.29	32 feces 0 urine	
38	M. 513	Cardiac chronic valvular	.....	37 feces †? urine	Lesion poorly compensated.
39	M. 536	Tuberculosis (general)	.....	14 feces	
40	S. 592	Carcinoma of stomach. metastases in liver; cholelithiasis.	.....	1—10 feces 2—20 feces 0 urine	
41	M. 152	Peritonitis (tubercular)	0.6		

† Trace †? Slight trace.

STUDY XXII: THE EFFECT OF THEOBROMIN SODIUM SALICYLATE IN ACUTE EXPERIMENTAL NEPHRITIS, AS MEASURED BY THE EXCRETION OF PHENOLSULPHONEPHTHALEIN *

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The therapeutic efficacy of diuretic drugs on patients with acute nephritis has been discussed by most writers in their description of methods of management of acute nephritis. The views expressed have been based largely on clinical observation, and there has been relatively little experimental evidence[1] accumulated in support of the claims made for the usefulness, within certain limitations, of diuretic drugs in acute nephritis. Inasmuch as clinical observation of acute nephritis is much hampered by the infrequency of uncomplicated cases and by the difficulties in determining whether any two patients actually present comparable renal lesions, it has seemed desirable to have more observations under experimental conditions in which some of the factors are controllable in the hope that gradually data may be accumulated as a basis for a more efficient method of treating acute nephritis. The following experiments are reported for this reason. Though inconclusive in many respects, it is hoped that they may throw some slight light on the problem and at least be helpful to other investigators by showing what has happened to these animals under the conditions of the experiment.

The experiments here reported concern themselves with one diuretic (theobromin sodium salicylate or diuretin*) used in one form of

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* From the Laboratory of the Theory and Practice of Physic, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

* This is one of a series of studies on experimental cardiorenal disease. Study I, Smith: Boston Med. and Surg. Jour., 1908, clviii, 696; Study II, Christian: Boston Med. and Surg. Jour., 1908, clix, 8; Study III, Christian: Jour. Am. Med. Assn., 1909, liii, 1792; Studies IV-XV, Christian, Smith and Walker: THE ARCHIVES INT. MED., 1911, viii, 468-551; Study XVI, Christian and O'Hare: THE ARCHIVES INT. MED., 1913, xi, 517; Studies XVII and XVIII, O'Hare: THE ARHIVES INT. MED., 1913, xii, 49, 61; Study XIX, Christian and O'Hare: Jour. Med. Research, 1913, xxviii, 227; Study XX, Walker and Dawson: THE ARCHIVES INT. MED., 1913, xii, 171; Study XXI, Fitz: THE ARCHIVES INT. MED., 1914, xiii, 945.

1. See Study XXI by R. Fitz (THE ARCHIVES INT. MED., 1914, xiii, 945) for a report of the immediate effects of theobromin sodium salicylate and theocin in experimental nephritis and for a review of other experimental work on the effects of diuretics.

* The preparation used throughout these experiments was made by Knoll & Co., and purchased from retail druggists under the name "diuretin."

acute nephritis (that produced by uranium nitrate) in a single laboratory animal (rabbit). Forty-nine animals were utilized and they were kept under similar conditions in metabolism cages on a diet of carrots, oats and water. The amount of each food taken by the rabbit varied with the animal's appetite, but all were measured. The urine was collected and measured in seventy-two- or twenty-four-hour periods. The uranium nitrate was given subcutaneously in doses of 3.5, 1.1, 0.5 and 0.25 mg. per kilogram of body weight, respectively, to different groups of animals. Forty-eight hours later theobromin sodium salicylate was

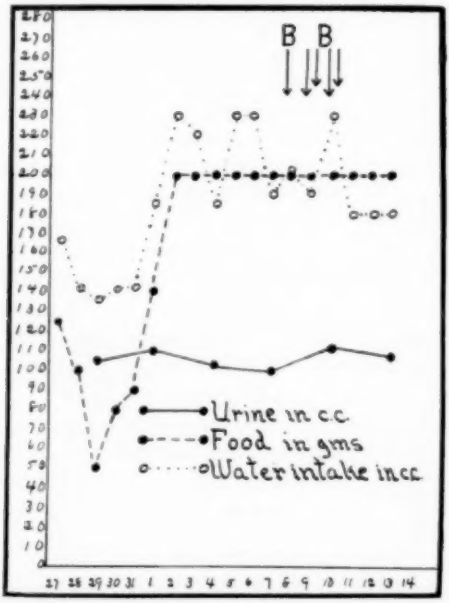


Chart 1.—Rabbit 86. *B*, theobromin sodium salicylate, 14 mg. per kilogram of body weight.*

given subcutaneously to a portion of these animals in a dose (14 mg. per kilogram of body weight) comparable to the therapeutic dose for man, and this was repeated in most cases twice daily for several days. The phenolsulphonephthalein excretion was determined at intervals; the phenolsulphonephthalein was given intramuscularly in a dose of 6 mg., and the urine for quantitation of the phenolsulphonephthalein excretion was obtained by catheterization with thorough washing out of the bladder; quantitation was carried out by the usual colorimetric method.

* Numerals along bottom of charts indicate days of the month.

The rabbits were studied in small groups at different periods between May, 1913, and April, 1914, and these groups were obtained from several dealers; consequently, in order to reduce the variants to a minimum, only animals within the several groups have been compared.

As a preliminary control, normal rabbits were given theobromin sodium salicylate in the way described. The result was practically nil, as shown by the chart[2] of Rabbit 86 (Chart 1). Other animals showed the same thing.

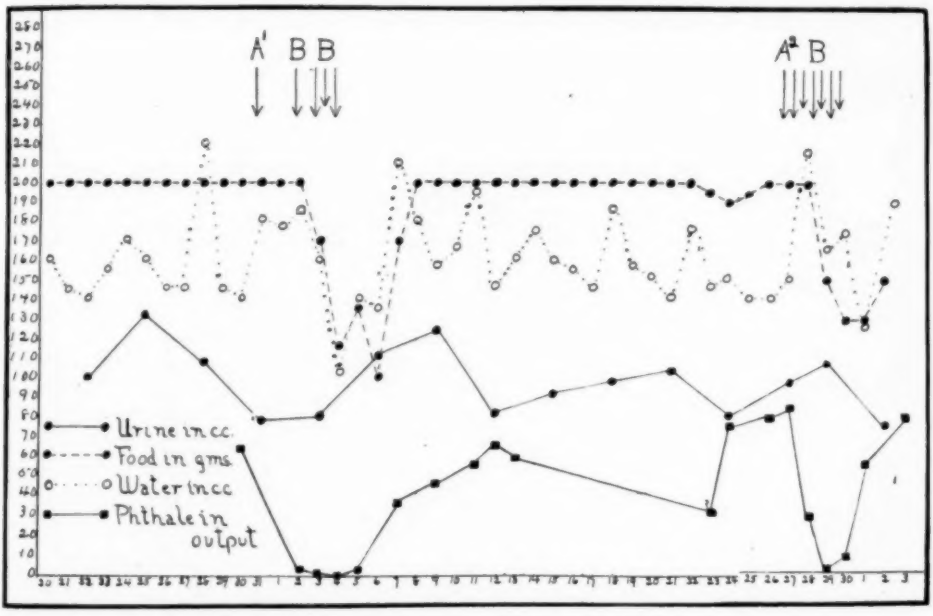


Chart 2.—Rabbit 686. Period of phenolsulphonephthaein excretion, one hour, 33 minutes. A^1, uranium nitrate, 3.5 mg. per kilogram of body weight. A^2, uranium nitrate, 1.1 mg. per kilogram. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

In the first series 3.5 mg. of uranium nitrate per kilogram of body weight was given to six animals (Rabbits 686, 687, 688, 689, 691 and 692) with results as shown in illustrative charts of a few rabbits[3] (Charts 2 and 3). This amount of uranium nitrate produces a severe

2. In all charts "water intake" includes water content of carrots calculated as 88 per cent. of total weight of carrots eaten.

3. Owing to expense of reproduction only a few of the charts which were made of each rabbit have been printed.

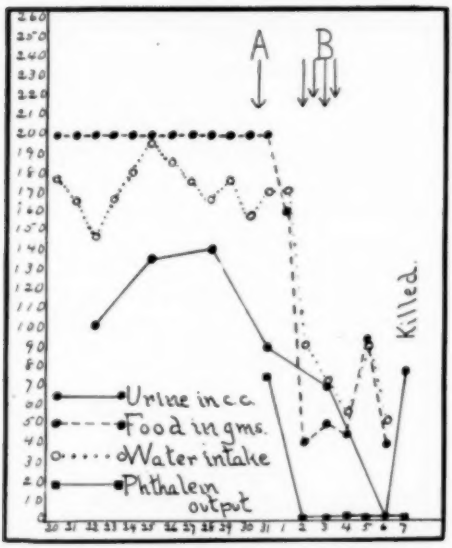


Chart 3.—Rabbit 688. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate, 3.5 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

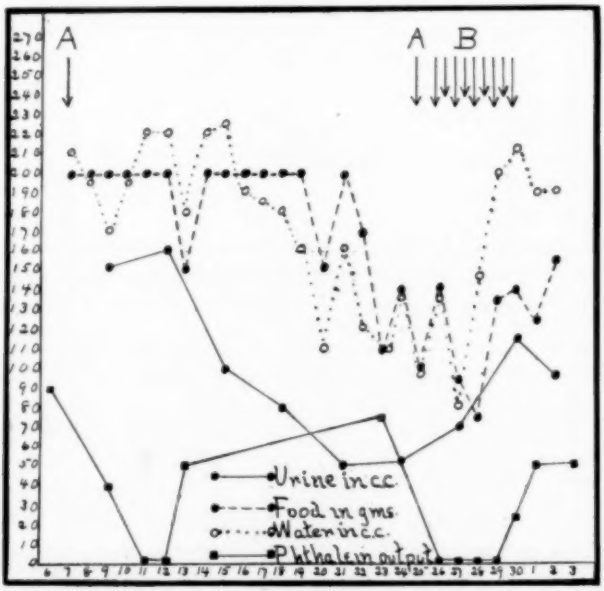


Chart 4.—Rabbit 701. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate, 1.1 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

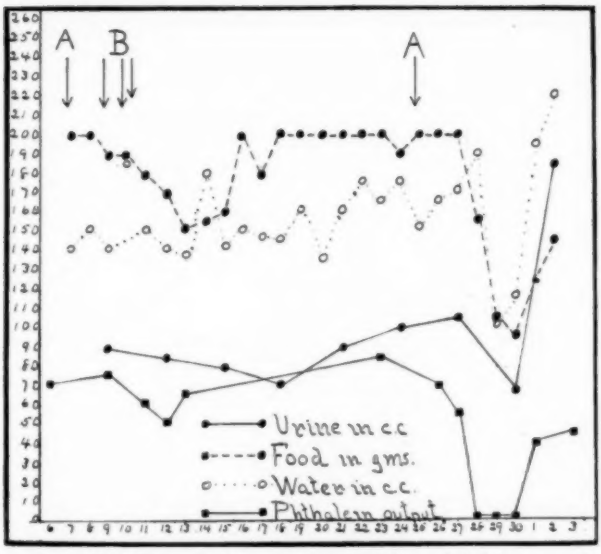


Chart 5.—Rabbit 702. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate 1.1 per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

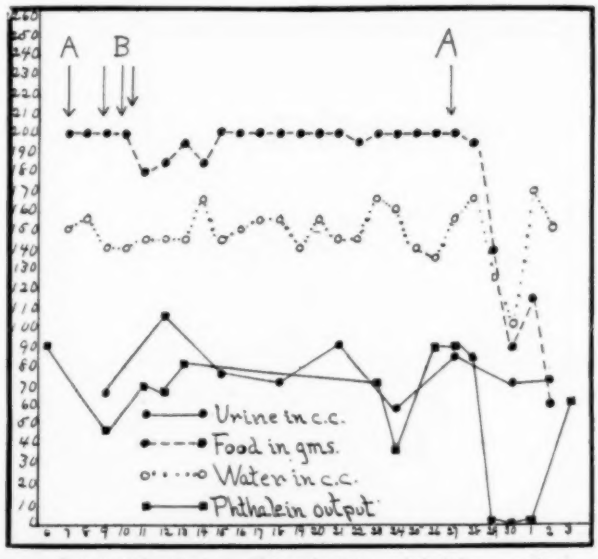


Chart 6.—Rabbit 705. Period of phenolsulphonephthalein excretion, one hour, thirty minutes. *A*, uranium nitrate, 1.1 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

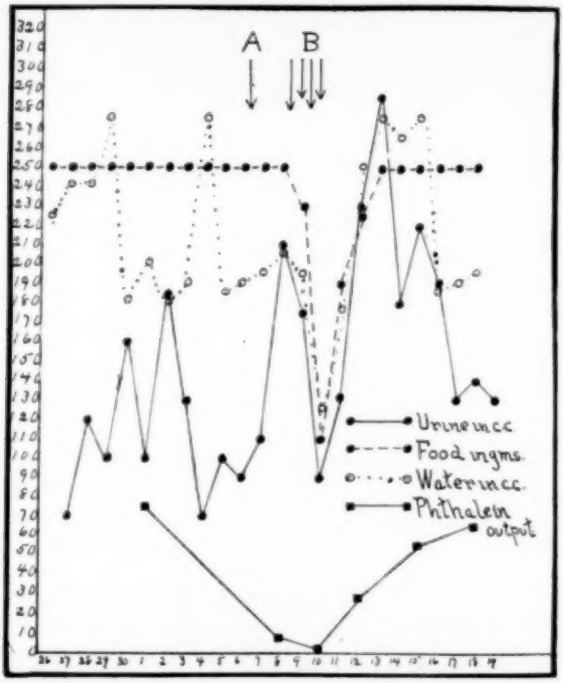


Chart 7.—Rabbit 816. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate, 0.5 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

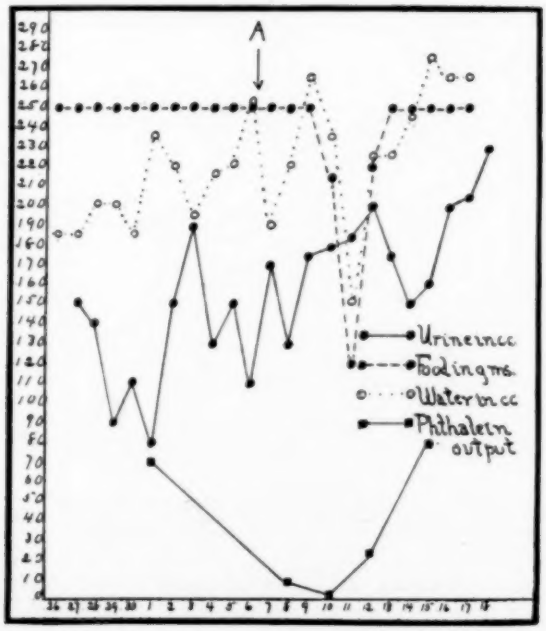


Chart 8.—Rabbit 819. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate, 0.5 mg. per kilogram of body weight.

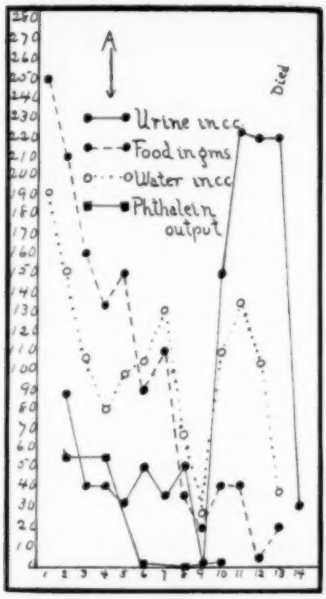


Chart 9.—Rabbit 790. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate, 0.5 mg. per kilogram of body weight.

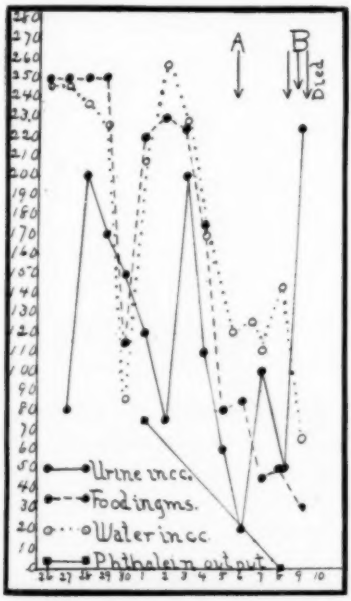


Chart 10.—Rabbit 815. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium nitrate, 0.5 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

usually fatal acute nephritis (see Christian and O'Hare[4] for average duration of life and lesion produced with and without theobromin sodium salicylate), and in these six rabbits all died in a short time, except one (Rabbit 686, Chart 2), to which theobromin sodium salicylate was given and which subsequently survived a smaller dose of uranium nitrate. In the five animals which died, those with and with-

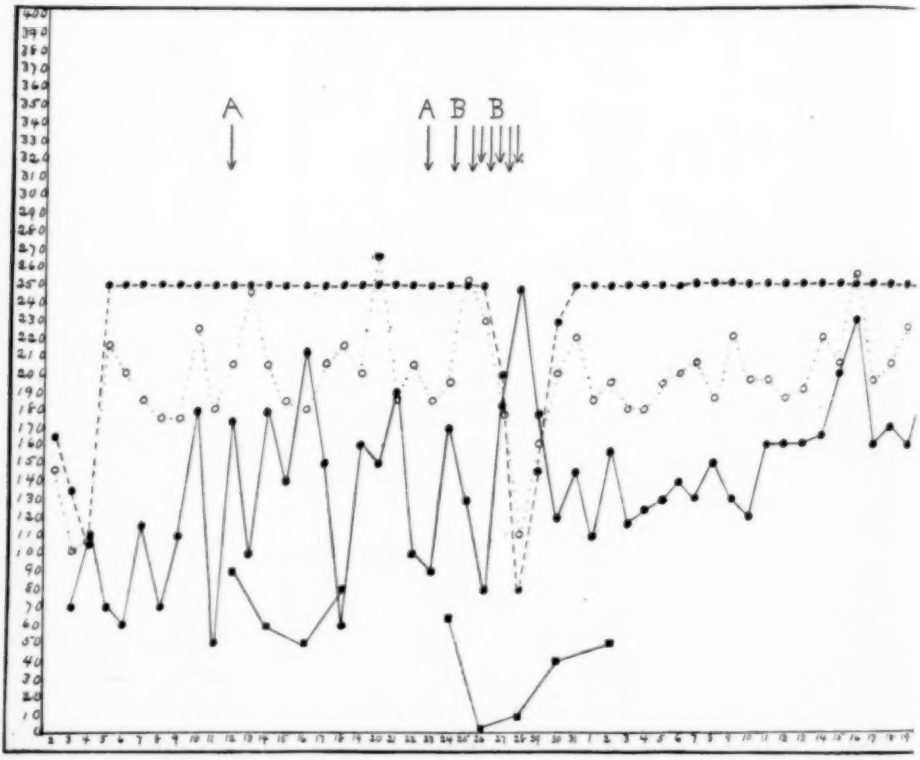
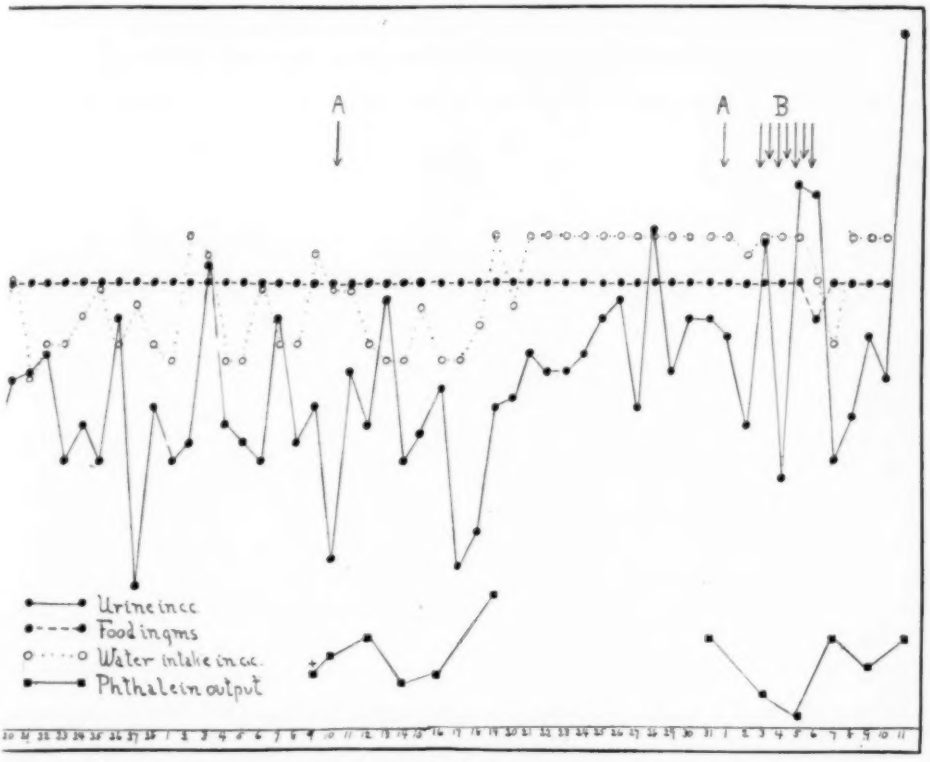


Chart 11.—Rabbit 849. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium

out theobromin sodium salicylate showed the same curve of phenolsulphonephthalein excretion, indicating a marked disturbance of function uninfluenced by theobromin sodium salicyate, though in one rabbit (688, Chart 3) a diuresis immediately preceded death. Whether or not theobromin sodium salicylate was responsible for the survival of

4. Christian, Henry A., and O'Hare, James P.: A Study of the Therapeutic Value of a Diuretic (Theobromin Sodium Salicylate or Diuretin) in Acute Experimental Nephritis (Study XVI), THE ARCHIVES INT. MED., 1913, xi, 517.

Rabbit 686 cannot be determined. It is known that rabbits vary in their susceptibility to uranium nitrate, and this may represent an unusual degree of natural resistance. This was observed in several rabbits of a previous series (Christian and O'Hare[4]), although in most of the rabbits in that study with severe nephritis theobromin sodium salicylate shortened life.



nitrate, 0.25 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

In the second (Rabbits 701, 702, 703, 704 and 705), third (Rabbits 707-708), fourth (Rabbits 709-716) and fifth (Rabbits 744-752) series of animals 1.1 mg. of uranium nitrate per kilogram of body weight was given, with results as shown in illustrative charts of some of the rabbits (Charts 4, 5 and 6). In two series the urine was collected at seventy-two-hour intervals, and in two at twenty-four-hour intervals. Of the second series, Rabbits 701, 702 and 705 received uranium nitrate twice nine days apart, once followed by theobromin sodium salicylate. These

rabbits (701, 702 and 705, Charts 4, 5 and 6) suggest a slight beneficial effect of theobromin sodium salicylate on renal function as measured by phenolsulphonephthalein excretion, but this effect is apparent rather than real when allowance is made for a probably more intense action of the second dose of uranium in an animal that a short time previously has had an acute renal lesion produced by the same dose of uranium nitrate.

If the curve of phenolsulphonephthalein excretion in all of the twenty-four animals of Series 2 to 5 is studied, it is seen that in a

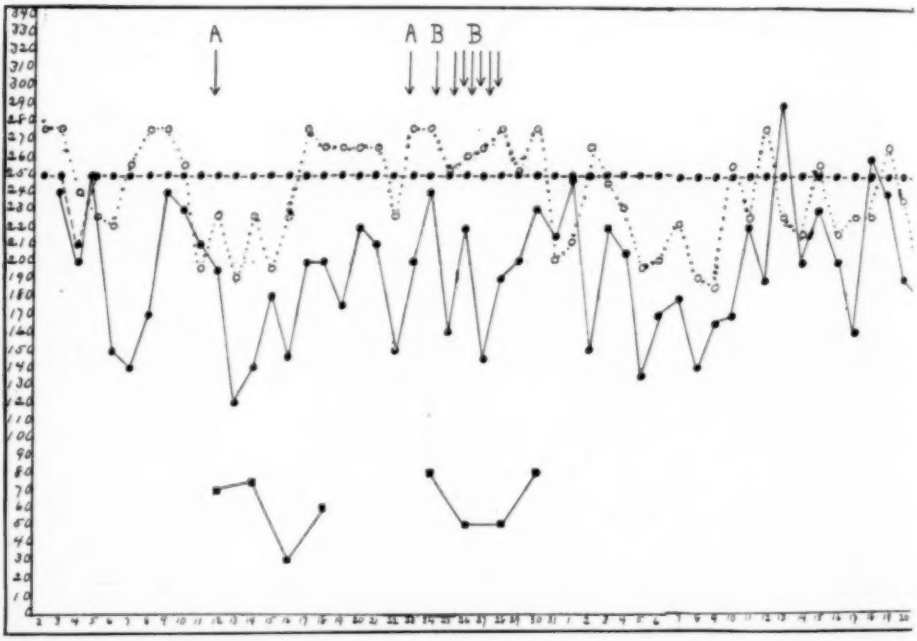
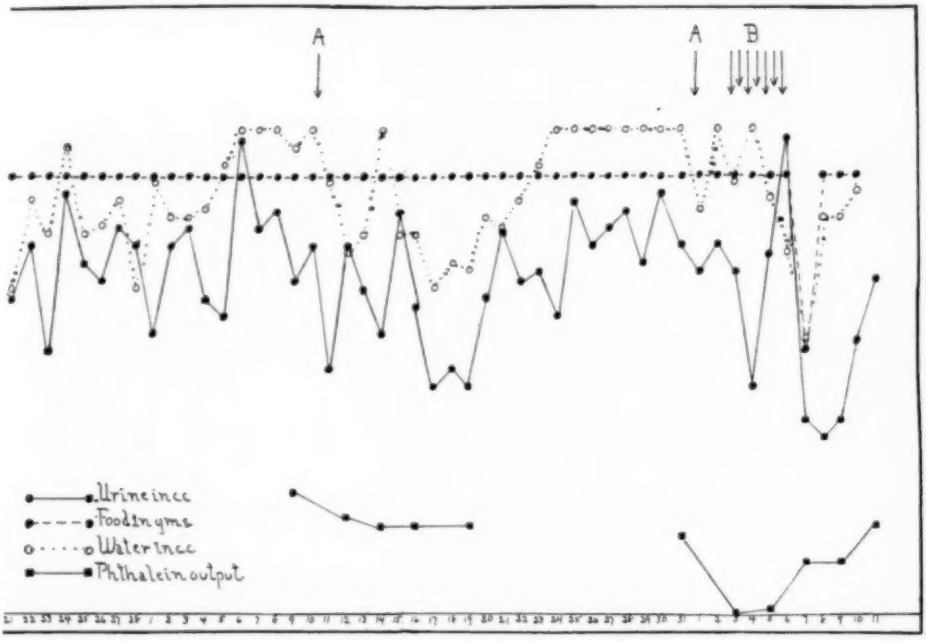


Chart 12.—Rabbit 850. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium

number theobromin sodium salicylate appears to have a slight beneficial action as expressed either by a slowed fall or a more prompt return to the normal phenolsulphonephthalein output. This is offset, however, by the fact that of the six rabbits that died, four had been given theobromin sodium salicylate. The amount of uranium given these rabbits, 1.1 mg. per kilogram of body weight, caused a severe nephritis in most, as shown by the 25 per cent. mortality, the marked loss of appetite, the decreased urine output, and the fall in phenolsulphonephthalein output to mere traces. In severe acute nephritis as shown by these series, as

well as by Series 1, it does not appear that theobromin sodium salicylate exerts any evident beneficial action on renal function as measured by phenolsulphonephthalein excretion; occasionally it seems to do good, but on the other hand, occasionally it seems to do harm. Consequently, it may be said that its use in rabbits with so severe an acute nephritis is a questionable therapeutic measure.

Examination of the charts shows that diuresis, though common, is not constant under the conditions of these experiments, and that it may occur a few days after the uranium is given, whether or not a diuretic



nitrate, 0.25 mg. per kilogram of body weight. *B*, theobromin salicylate, 14 mg. per kilogram.

is used. What is quite striking is that urine output and renal function as measured by phenolsulphonephthalein excretion do not necessarily run parallel, and sometimes animals with marked diuresis die.* In these animals phenolsulphonephthalein output is distinctly a better prognostic sign than urine output.

In Series 6 (Rabbits 789, 790, 791) and 7 (Rabbits 815-819) still smaller doses of uranium nitrate were used, 0.5 mg. per kilogram of body weight (for results see Charts 7, 8, 9 and 10 of illustrative ani-

* None of the charts selected for printing from these series show this but it is shown in Charts 9 and 10 of the next series.

mals). Two rabbits, 790 and 815 (Charts 9 and 10), one with and one without theobromin sodium salicylate, show a marked diuresis preceding death. In these series the charts show a slightly more evident beneficial effect from theobromin sodium salicylate, though this is really too slight to be considered of much importance and might be easily a matter of coincidence rather than cause and effect. Since the lesion in most of these animals is a severe one, for three out of nine died, one having received theobromin sodium salicylate, two not, it seemed desirable to use still smaller doses of uranium nitrate.

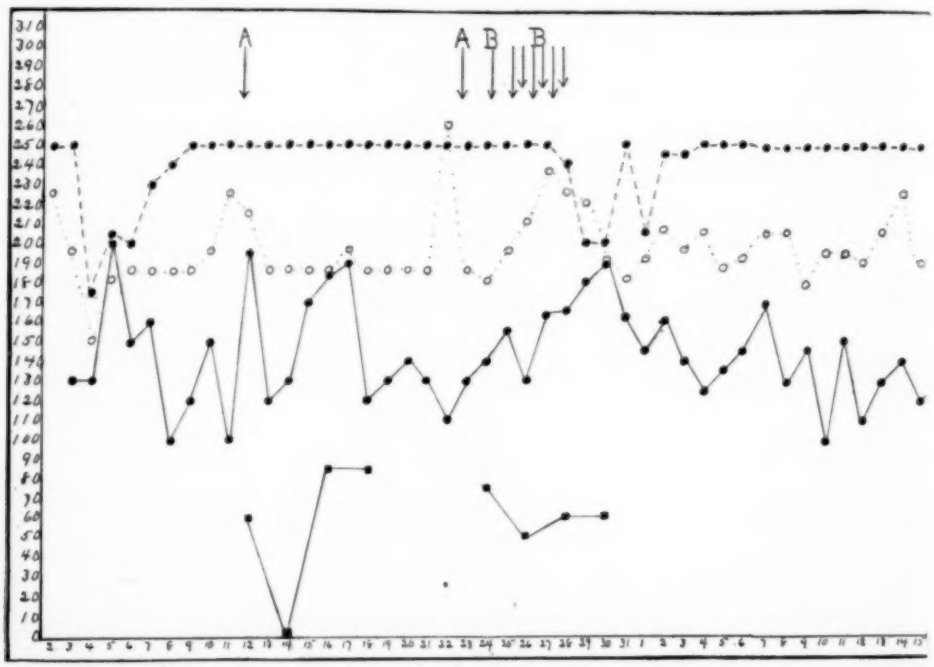
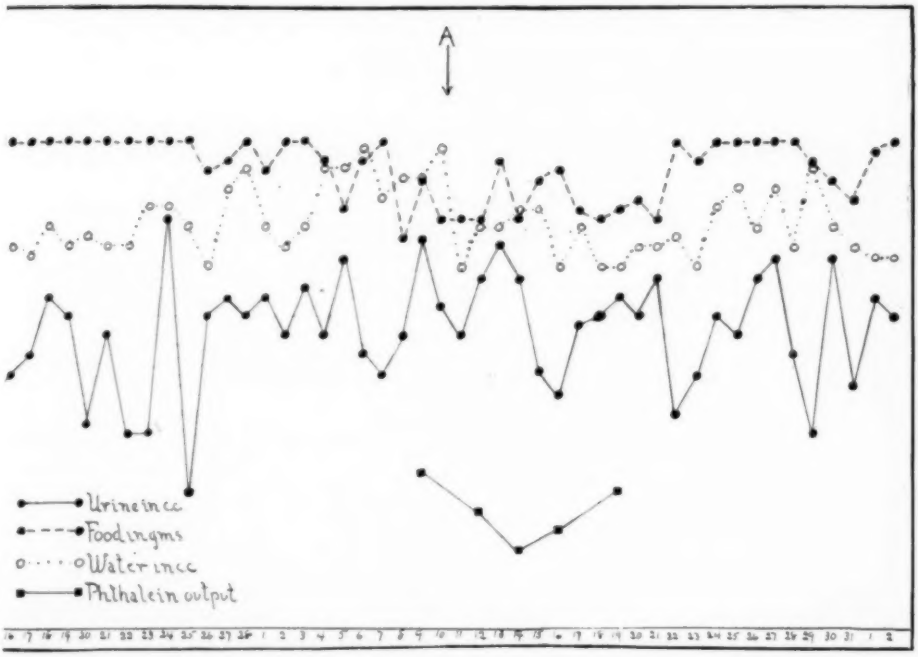


Chart 13.—Rabbit 851. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium

In the last series (Series 8, Rabbits 849-854) 0.25 mg. of uranium nitrate per kilogram of body weight was used. Inasmuch as it seemed likely that this dose would not produce any profound change in the kidney not easily recoverable from, a slightly different method was followed in that uranium was repeated after a time interval thought to be long enough for recovery. With the first dose of uranium no rabbit received theobromin sodium salicylate, and this dose was used only as a test of the rabbit's susceptibility to uranium. One rabbit, 853, died even after this small dose of uranium. This animal showed a precritical

diuresis. Rabbits 849, 850, 851, 852 and 854 (Charts 11, 12, 13, 14 and 15) showed a very slight disturbance of renal function as evidenced by decreased output of phenolsulphonephthalein. That the disturbance was slight is shown by the prompt return to normal of the phenolsulphonephthalein excretion and the failure of the rabbits to have any decrease in appetite. One rabbit (852, Chart 14) showed no decrease in phenolsulphonephthalein, but a slight loss in appetite. After ten days, uranium was repeated to the five remaining rabbits, and to three of these theobromin sodium salicylate was subsequently given. In these, in general theobromin sodium salicylate appeared to decrease slightly



nitrate, 0.25 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

functional disturbance as evidenced by phenolsulphonephthalein excretion, but not to have much effect as indicated by the animals' appetite. All five animals showed moderately increased diuresis subsequent to the uranium, but this diuresis was not definitely influenced by theobromin sodium salicylate.

Forty-six days following the second dose of uranium, the same animals received a third dose of uranium. To the two not receiving theobromin sodium salicylate previously this drug was given. In

Rabbits 849 (Chart 11) and 850 (Chart 12) without theobromin sodium salicylate, phenolsulphonephthalein excretion was slightly less depressed after uranium than had previously been the case when theobromin sodium salicylate had followed the uranium. In Rabbit 851 (Chart 13) the reverse was true. In Rabbit 852 (Chart 14) with theobromin sodium salicylate the curve of phenolsulphonephthalein excretion showed a delayed fall and a slightly more abrupt rise than previously

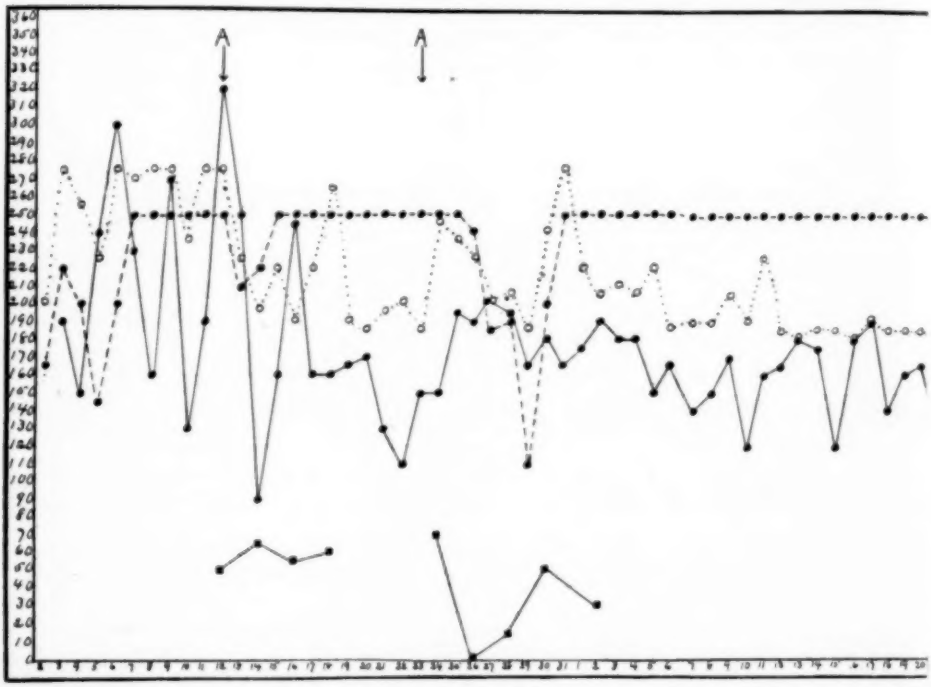


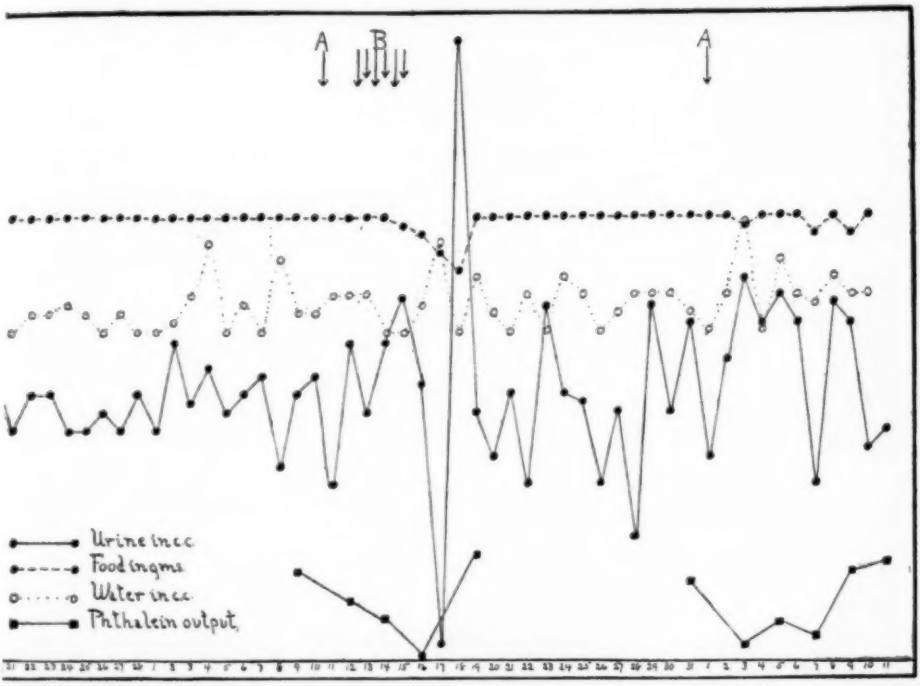
Chart 14.—Rabbit 852. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium

without theobromin sodium salicylate, while in Rabbit 854 (Chart 15) with theobromin sodium salicylate the phenolsulphonephthalein curve showed much less of a fall than had been the case in this rabbit without theobromin sodium salicylate.

If we compare the phenolsulphonephthalein excretion with and without theobromin sodium salicylate in these rabbits after the second and third dose of uranium, the curves taken all together show a slightly better excretion with theobromin sodium salicylate than without it. The difference, however, is slight, for it appeared in favor of theo-

bromin sodium salicylate in but three out of five experiments, and in these the differences were quantitatively slight.

Finally, in three rabbits, 849, 850 and 852 (Charts 11, 12 and 14) a fourth injection of uranium was given twelve days following the third, and after this dose theobromin sodium salicylate was given to two animals. Here the curves were distinctly though slightly against this diuretic improving renal function.



nitrate, 0.25 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

If the last group with very slight degrees of renal disturbance is viewed as a whole and if allowance is made for some probable variation in effect from so small a dose of uranium, to say nothing of variations in results obtained at times without explainable cause in all of the observations here reported, the conclusion would seem justifiable that even in very slight degrees of acute experimental (uranium) nephritis in the rabbit there is little evidence of any beneficial action from theobromin sodium salicylate on renal function as measured by phenolsulphonephthalein excretion. It is equally true that there is little evi-

dence of any harmful action. Rather are the results suggestive of no constant action.

SUMMARY

So far as renal function may be judged from phenolsulphonephthalein excretion in acute experimental nephritis produced by uranium in the rabbit, there is no evidence that theobromin sodium salicylate exerts any constant beneficial action. In the severer forms there is almost no evidence of beneficial action; in the very mild forms there is occasionally evidence of beneficial action, but this is too inconstant to justify the conclusion that theobromin sodium salicylate really improves renal function even in the very mild forms of acute nephritis. As other experimental evidence (Christian and O'Hare[4]) has shown the injurious action of theobromin sodium salicylate in shortening the life of rabbits with severe acute experimental (uranium) nephritis, it would seem fair to conclude that there is considerable evidence against

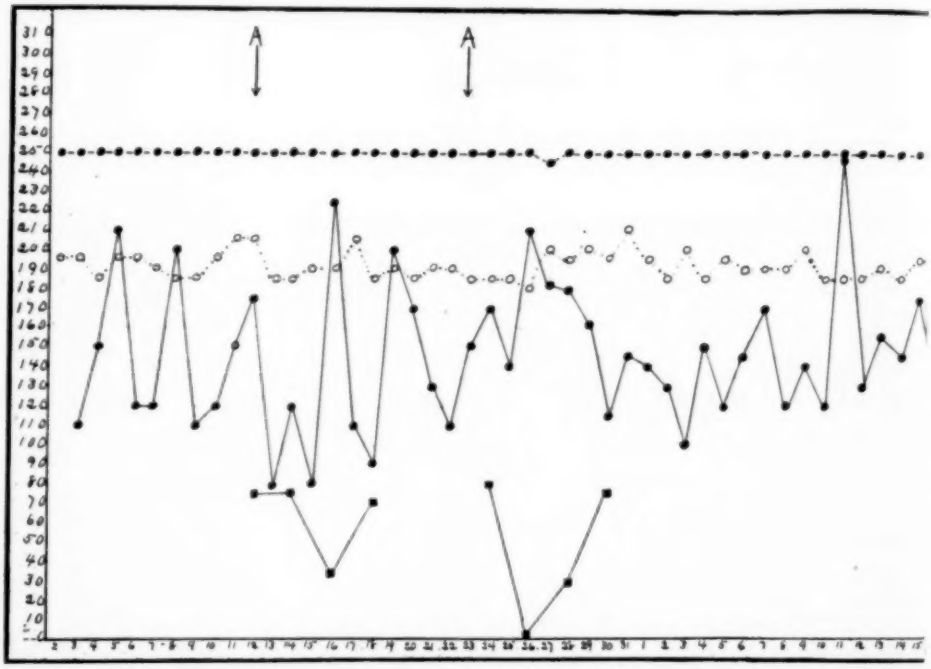
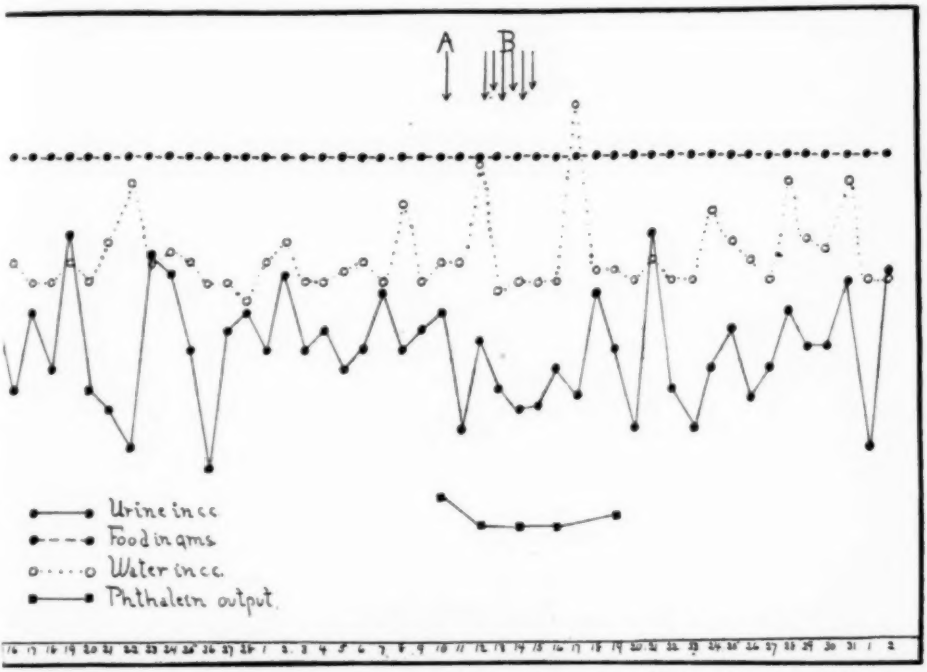


Chart 15.—Rabbit 854. Period of phenolsulphonephthalein excretion, one hour. *A*, uranium

the use of theobromin sodium salicylate in severe experimental nephritis, and very little in its favor in milder forms in which the conditions of experimentation involve observation over several days. It hardly seems necessary to add that it should be clearly kept in mind that the evidence adduced above concerns itself only with the rabbit, and the rabbit with acute nephritis of a single type, that produced by uranium, and that only one measure of renal function (phenolsulphonephthalein excre-



nitrate, 0.25 mg. per kilogram of body weight. *B*, theobromin sodium salicylate, 14 mg. per kilogram.

tion) is being used. The results obtained in the rabbit are in accord with the common clinical teaching that diuretics are not indicated in acute nephritis in man; but they are no proof of the correctness of this teaching, for results obtained in rabbits cannot be directly read in terms of man. However, they would seem to lend some further support to the view based on clinical observation that diuretics are not indicated in acute nephritis.

Peter Bent Brigham Hospital.

NITROGEN METABOLISM AND THE SIGNIFICANCE OF THE NON-PROTEIN NITROGEN OF THE BLOOD IN EXPERIMENTAL URANIUM NEPHRITIS *

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INTRODUCTION

It has been known for a long time that, in the course of any nephritis, there are certain periods when the urinary constituents are normal in amount as compared with the intake, and other intervals when they may be increased or diminished. To fathom the reasons for these changes in excretion seemed, until recently, an impossible task. Von Noorden[1] begged the question by characterizing the metabolism of nephritis as "bizarre and inexplicable," and many others have followed his example. Observations have been generally based on the assumption that nephritis, whether involving the glomeruli or the tubules, has only one effect on function: a diminished excretory activity of the part. Such an assumption lacks proof and is not in accord with the clinical conditions as they are generally acknowledged to exist. During the past few years the study of these questions has yielded very suggestive results. The following experiments were undertaken with the idea of enlarging on these so far as the nitrogen metabolism of nephritis is concerned.

METHODS

Dogs were kept in metabolism cages and fed on the required diet. The latter consisted of hashed lean meat, lard, cracker meal, bone-ash and water, given in weighed or measured quantities. Urea and sodium chlorid were added in certain instances. All animals were rejected that did not take kindly to the cage life and food, or that showed any pathologic quantities of albumin in the urine.

The nitrogen was determined by the Kjeldahl process, the sodium chlorid according to Volhard, the total sulphur by Benedict's method,[2] glucose by Benedict's modification[3] of Fehling's method, the non-

* Submitted for publication July 1, 1914.

* From the Department of Medicine and the Laboratory of the Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York. Under the auspices of the Edward N. Gibbs' Prize Fund of the New York Academy of Medicine.

1. Von Noorden: Handbuch. der Pathologie des Stoffwechsels, Berlin, 1906, i, 1002.
2. Benedict: Jour. Biol. Chem., 1909, vi, 363.
3. Benedict: Jour. Biol. Chem., 1911, ix, 57.

protein nitrogen of the blood according to the procedure of Folin and Denis,[4] and the albumin by the Esbach test.

All the urinary determinations, except those for glucose and albumin, were made on an albumin-free specimen. The urine was acidified with acetic acid, boiled, cooled, made up to double the original volume, filtered and the filtrate used for the analyses. The uranium nitrate was injected subcutaneously in 1 per cent. solution in the amounts noted in the individual protocols. Blood was obtained by aseptic puncture of the heart. Water was given by stomach-tube when necessary. Forty metabolism experiments were performed. Limitation of space forbids the citation of all the protocols.

THE LESIONS OF URANIUM NEPHRITIS

The examination of the kidneys in these animals yielded anatomic pictures which were in full accord with the observations previously published.[5] The tubules showed the most marked changes. The convoluted tubules, especially, showed extensive granular degeneration to be followed by necrosis. Many of the glomeruli were markedly congested, but gave no other evidence of disease. Hence, this form of experimental nephritis has been classified as a tubular nephritis. Though the anatomic study of these kidneys did not demonstrate any notable involvement of the glomeruli, the work of Schlayer and his associates[6] on rabbits, confirmed by Pearce, Hill and Eisenbrey[7] on dogs, proves that there is a functional change in the vascular apparatus, that is, of the glomeruli of the kidney, which may be of far-reaching significance in modifying the activity of that organ. Christian[8] has noted hyaline degeneration of the walls of the capillaries of the glomerular tuft. These changes are so very limited in extent that it does not appear probable that they have an appreciable influence in changing the excretory power of the kidney.

NITROGEN ELIMINATION IN THE URINE—RETENTION

By using large doses of uranium nitrate it was found that the nitrogen in the urine becomes diminished and is consequently retained. This is well shown in Dog 25, Table 1. Such a retention of nitrogen

4. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527.

5. Kraus, Walter M.: The Effect of Uranium Nephritis on the Excretion of Creatinin, Uric Acid and Chlorids, and the Effect of Creatinin Injections during Uranium Nephritis, THE ARCHIVES INT. MED., 1913, xi, 613, gives a summary of the literature on this subject.

6. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xcviii, 17. Schlayer, Hedinger and Takayasu: ibid., 1907, xci, 59.

7. Pearce, Hill and Eisenbrey: Jour. Exper. Med., 1910, xii, 196.

8. Christian, Henry A., Smith, R. M., and Walker, I. Chandler: Experimental Cardiorenal Disease, THE ARCHIVES INT. MED., 1911, viii, 468.

TABLE 1.—Result of Experiment with Dog 25*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Weight kilos	Water Intake c.c.	Volume of Urine c.c.	Urinary Nitrogen gm.	Urinary Sulphur gm.	Ratio N : S	Remarks
Days								
Control...	0.0	8.53	360	450	8.47	0.52	16 : 1	
Control...	0.0	8.58	360	485	8.47	0.45	19 : 1	
Control...	0.0	8.54	360	510	8.01	0.50	16 : 1	
Control...	0.0	8.55	360	445	8.22	0.50	16 : 1	0.10 gm. uranium nitrate injected subcutaneously.
Test								
1	1.5	8.48	360	530	6.21	0.52	12 : 1	
2	...	8.08	360	730	....	....	.....	Vomited.
3	2.2	8.11	560	685	6.31	0.42	15 : 1	
4	2.0	8.19	660	635	6.21	0.44	14 : 1	
5	...	7.58	360	910	....	....	.....	Vomited.
6	1.8	7.48	660	500	4.32	0.30	14 : 1	Vomited.

* The daily diet of this animal consisted of hashed ox-heart, 225 gm.; cracker dust, 60 gm.; lard, 10 gm.; bone ash, 10 gm.; water as noted under "water" in table.

TABLE 2.—Result of Experiment with Dog 23*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Volume Urine c.c.	Glucose		Urinary Nitrogen gm.	Urinary Sodium Chlorid gm.	Urinary Sulphur gm.	Ratio N : S	Remarks
			Pct.	Gm.					
Days									
Control...	0.0	282	0.0	0.0	2.82	1.40	0.14	20 : 1	
Control...	0.0	318	0.0	0.0	2.69	1.60	0.14	20 : 1	
Control...	0.0	330	0.0	0.0	2.88	1.46	0.14	21 : 1	
Control...	0.0	266	0.0	0.0	3.10	1.11	0.13	23 : 1	
Control...	0.0	320	0.0	0.0	3.06	1.50	0.13	23 : 1	
Test									
1	Trace	310	...	...	3.34	1.32	0.16	21 : 1	0.004 gm. uranium nitrate injected subcutaneously.
2	1.0	360	0.6	2.2	3.20	0.89	0.21	16 : 1	0.004 gm. uranium nitrate injected subcutaneously.
3	3.0	565	1.6	9.0	3.58	0.50	0.28	13 : 1	0.004 gm. uranium nitrate injected subcutaneously.
4	3.0	550	2.8	15.4	4.34	0.58	0.27	16 : 1	0.004 gm. uranium nitrate injected subcutaneously. Vomited a little food.
5	2.0	595	2.3	13.6	4.36	0.82	0.26	17 : 1	0.004 gm. uranium nitrate injected subcutaneously. Vomited a little froth.

* The daily diet of this animal consisted of chopped beef-heart, 120 gm.; cracker dust, 32 gm.; lard, 24 gm.; bone ash, 8 gm.; sodium chlorid, 1 gm.; water, 290 c.c. This diet was fed for nine days before the collection of urine was begun.

TABLE 3.—Results of Experiment with Dog 10*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Volume Urine c.c.	Glucose		Urinary Nitrogen gm.	Nitrogen Balance †	Urinary Sulphur gm.	Ratio N : S	Remarks
			Pct.	Gm.					
Days §									
Control...	0.0	300	0.0	0.0	5.13	—0.33	0.33	16 : 1	
Control...	0.0	250	0.0	0.0	5.13	—0.33	0.33	16 : 1	
Control...	0.0	250	0.0	0.0	4.52	+0.28	0.29	16 : 1	
Control...	0.0	228	0.0	0.0	4.52	+0.28	0.29	16 : 1	
Control...	0.0	240	0.0	0.0	4.78	—0.02	0.30	16 : 1	
Control...	0.0	280	0.0	0.0	4.78	—0.02	0.30	16 : 1	0.01 gm. uranium nitrate injected subcutaneously.
Test									
1	0.5	290	0.0	0.0	4.48	+0.32	0.29	15 : 1	
2	2.0	258	0.2	0.5	4.73	+0.07	0.32	15 : 1	
3	2.8	393	0.8	3.0	4.69	+0.11	0.34	14 : 1	
4	3.0	410	0.9	3.7	4.28	+0.52	0.31	14 : 1	
5	2.0	342	1.3	4.3	4.42	+0.38	0.31	14 : 1	
6	1.8	302	1.5	4.6	5.01	—0.21	0.31	16 : 1	
7	1.5	290	1.3	3.8	5.60	—0.80	0.30	19 : 1	
8	1.8	310	1.8	5.5	5.98	—1.18	0.29	20 : 1	
9	1.3	385	1.6	6.0	6.96	—2.16	0.33	21 : 1	
10	1.8	350	0.5	1.7	5.83	—1.03	0.27	22 : 1	
11	1.3	345	0.7	2.3	5.88	—1.08	0.26	22 : 1	
12	0.8	314	0.4	1.3	5.47	—0.67	0.26	21 : 1	
13	0.5	280	0.2	0.5	4.64	+0.16	0.23	20 : 1	
14	0.3	260	0.0	0.0	4.81	—0.01	0.24	20 : 1	
15	0.5	324	†	†	5.69	—1.89	0.33	17 : 1	
16	0.3	248	0.0	0.0	4.13	+0.67	0.22	18 : 1	
17	0.3	264	0.0	0.0	4.68	+0.12	0.26	18 : 1	
18	Trace	330	0.0	0.0	5.63	—0.83	0.32	18 : 1	
19	0.0	274	0.0	0.0	4.99	—0.19	0.28	18 : 1	
20	0.0	324	0.0	0.0	5.44	—0.65	0.29	19 : 1	

* The daily diet of this animal consisted of hashed lean beef, 120 gm.; cracker dust, 32 gm.; lard, 24 gm.; bone ash, 8 gm.; water, 280 c.c. This diet, containing 5.30 gm. of nitrogen, was fed for twelve days before specimens of urine were collected for analysis.

† Trace.

‡ 0.5 gm. nitrogen were calculated as being excreted in the feces.

§ During the control days analyses were made every forty-eight hours; subsequently every twenty-four hours.

TABLE 4.—Result of Experiment with Dog 15*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Weight kilos	Volume of Urine c.c.	Glucose		Urinary Nitrogen gm.	Nitrogen Balance † gm.	Remarks
				Pct.	Gm.			
Days								
Control...	0.0	15.40	860	0.0	0.0	23.43	—0.95	
Control...	0.0	15.40	675	0.0	0.0	20.02	+2.46	
Control...	0.0	15.55	635	0.0	0.0	19.37	+3.11	
Control...	0.0	15.40	870	0.0	0.0	29.28	—6.80	
Control...	0.0	15.54	650	0.0	0.0	20.22	+2.26	0.15 gm. uranium nitrate injected subcutaneously..
Test								
1	0.0	15.43	840	0.0	0.0	23.71	—1.23	
2	1.5	15.36	870	‡	‡	21.00	+1.48	
3	2.8	15.20	870	...	...	23.38	—0.90	Vomited; urine clear.
4	2.0	14.94	974	2.0	19.5	21.47	+1.01	
5	3.0	14.84	838	2.2	18.4	.....	.....	Vomited; urine mixed with vomit.
6	1.8	14.54	1,090	2.8	30.5	29.55	—7.07	Vomited; urine clear.
7	1.0	14.46	875	2.3	20.1	24.05	—1.57	
8	1.0	13.79	950	2.8	11.9	24.24	—1.76	Vomited; urine clear.
9	2.0	13.74	890	3.1	27.6	28.14	—5.66	
10	2.0	13.87	815	2.2	17.9	25.27	—2.79	
11	2.5	14.03	595	2.8	16.7	19.94	+2.54	
12	1.8	14.13	685	1.9	13.0	25.06	—2.58	
13	1.0	14.40	640	1.3	8.3	23.71	—1.23	
14	0.5	14.59	605	0.4	2.4	23.09	—0.61	
15	Trace	14.88	535	0.0	0.0	20.51	+1.97	
16	0.0	15.06	645	0.0	0.0	21.50	+0.98	
17	0.0	15.12	730	0.0	0.0	20.54	+1.94	
18	0.0	15.26	650	0.0	0.0	18.04	+4.44	
19	0.0	15.29	765	0.0	0.0	19.74	+2.74	

* The daily diet of this animal consisted of chopped lean beef, 286 gm.; cracker dust, 60 gm.; lard, 30 gm.; bone ash, 15 gm.; sodium chlorid, 2.55 gm.; urea, 11.54 gm.; water, 750 c.c. This diet containing 22.98 gm. of nitrogen was fed for ten days before the collection of urine was begun.

† The amount of nitrogen calculated as being excreted in the feces was 0.5 gm. ‡ Trace.

has been found in various forms of experimental nephritis. Siegel[9] demonstrated this in uranium nephritis, Pearce, Hill and Eisenbrey[7] in experimental tubular nephritis. Austin and Eisenbrey[10] showed that "uranium, cantharidin and potassium chromate in larger doses impair the power of the kidney to eliminate nitrogen." Underhill,[11] and Underhill, Wells and Goldschmidt[12] obtained marked diminution in the excretion of nitrogen in tartrate nephritis, which proved to be a typical tubular nephritis, and Green[13] similar results in chromate nephritis.

There seems to be no doubt that kidney insufficiency in these cases is responsible for the retention of nitrogen. In this animal (Table 1), as throughout these experiments, the quantity of urine excreted was large in amount, and the retention of any urinary constituent cannot be attributed to an oliguria or anuria. In this respect the dog differs widely from the rabbit, which has been a favorite subject for similar work.

NITROGEN ELIMINATION IN THE URINE — INCREASED EXCRETION

With smaller doses of uranium nitrate, yet sufficiently large to produce a distinct nephritis, as evidenced by the degree of albuminuria, the excretion of nitrogen in the urine becomes increased instead of diminished. This may be readily seen in Table 2, Dog 23; Table 3, Dog 10; Table 5, Dog 24; Table 6, Dog 31; Table 7, Dog 33; Table 9, Dog 34; Table 10, Dog 5; Table 11, Dog 27, and Table 14, Dog 1. The amounts of nitrogen excreted in these cases are considerable. Thus Dog 23, a small animal weighing 7.5 kilos, showed, on comparing the urine of the control with the experimental period, an average daily loss of 0.85 gm. of nitrogen during five days of uranium nephritis, that is, an increased excretion of 29.2 per cent. over the control days; Dog 10 (the feces being estimated and not determined), a negative nitrogen balance of 8.35 gm. in twenty days; Dog 34 (the nitrogen content of all the excreta being determined), a loss of 8.26 gm. in nine days, none of this loss occurring in the feces in which the nitrogen content was not increased above that of the control period, and only 0.70 gm. in the vomit.

Pohl,[14] working with rabbits, found a similar condition in subacute uranium nephritis. The increased excretion of water, nitrogen and sodium chlorid in his experiments was ascribed to "an irritation of the kidney." Austin and Eisenbrey[10] found that, in dogs, uranium and

9. Siegel: Ztschr. f. exper. Path. u. Therap., 1907, iv, 561.
10. Austin and Eisenbrey: Jour. Exper. Med., 1911, xiv, 366.
11. Underhill: Jour. Biol. Chem., 1912, xii, 115.
12. Underhill, Wills and Goldschmidt: Jour. Exper. Med., 1913, xviii, 347.
13. Green: Jour. Path. and Bacteriol., 1909, xiii, 296.
14. Pohl: Arch. f. exper. Path. u. Pharmakol., 1892, xxix, 282.

cantharidin in the smallest doses capable of producing a nephritis, tend to increase the elimination of nitrogen, probably by stimulating tissue catabolism. Beyond stating this as a surmise no proof of this contention is brought out. In the experiments of Austin and Eisenbrey larger doses of these drugs impaired the power of the kidney to eliminate nitrogen. This was not apparent unless the daily nitrogen intake was high, 1 gm. per kilo. An increase in the nitrogen fed does not necessarily produce a retention of nitrogen. Thus Table 4, Dog 15, gives the protocol of an animal weighing 15.5 kilos receiving 22.98 gm. of nitrogen (11.54 gm. as urea, the remainder in meat and cracker meal) and eliminating this amount without any difficulty; Table 14, Dog 1, shows how approximately 1 gm. of nitrogen per kilo is excreted without retention. In these experiments the severity of the nephritis appeared to be of far greater moment in producing retention of nitrogen than did the quantity of nitrogen fed. It is certain that a nephritis of considerable intensity may be produced without any manifestation of kidney insufficiency so far as the urinary nitrogen is concerned. Individual animals seem to vary greatly as to their susceptibility to the poison and it seems much more rational to measure the severity of the nephritis by the intensity of the symptoms, vomiting, etc., rather than by the dose of uranium given.

The accompanying chart expresses better than words the extreme variation of nitrogen excretion. The curves shown are all typical. Dog 23 showed an increased nitrogen elimination from the beginning of the nephritic period, Dog 25 a retention and Dog 10 a normal or slightly subnormal amount for the first few days, followed by a considerable increase. The last type of elimination is the one which was produced most frequently (many of the protocols are not given), the aim in most of these experiments being to work with an increased elimination of the nitrogen in the urine and to discover its significance.

NITROGEN ELIMINATION IN THE FECES

The quantity of nitrogen found in the feces did not vary from the normal, provided that there was no diarrhea. This is seen in Table 8, Dog 35 (only the first four days of the nephritic period should be taken into account; during the following days the animal refused food and the fecal nitrogen naturally diminished); Table 9, Dog 34, and Table 10, Dogs 5 and 7. These findings are in accord with those of Siegel[9] and Pearce, Hill and Eisenbrey.[7] It is, therefore, permissible, if the feces are of normal consistency, to estimate the nitrogen of the feces as has been done in calculating some of the nitrogen balances. When diarrhea does occur the amounts of nitrogen excreted through the intestines may be enormous. Table 7, Dog 33, shows an excretion

in the feces of 7.62 gm. of nitrogen during one day of diarrhea. This amount exceeded the quantity of nitrogen in the food by a small margin. It is worthy of note that the quantities of nitrogen in the feces and in the urine do not bear an inverse ratio to each other, but appear to run an independent course.

Comparative curves of excretion of urinary nitrogen as compared with amount of nitrogen of the control periods. The types of elimination shown. Arrow indicates time of uranium injection. Solid line across chart indicates level of urinary nitrogen during control period; curves above line, excess of excretion; below, retention. Line of dashes, Dog 10; dotted line, Dog 23; solid line, Dog 25.

THE CAUSE OF INCREASED NITROGEN EXCRETION

Two possibilities present themselves: (1) changes in the functional activity of the kidney, (2) increased protein catabolism. The old idea that in every case of nephritis an increased elimination of one of the urinary constituents is preceded by a retention, obviously cannot apply here.

1. *Changes in the Functional Activity of the Kidney.*—It is tempting to associate a definite renal lesion with a correspondingly clear-cut diminution in the excretion of one or more urinary constituents. When these vary so that they may be either increased or diminished, from the very outset of a nephritis, it becomes clear that such an idea must necessarily be revised. Schlayer[15] and his pupils have brought forward some most suggestive theories based on experimental evidence, as well as clinical observations to elucidate this point. They claim that a moderately severe lesion of the kidney parenchyma results in "hypersensitiveness," characterized by an overactivity of the part. Under these circumstances the kidney acts like a suction-cup in hastening the formation of urine. As the pathologic involvement becomes more complete the hypersensitiveness and overactivity diminish in direct ratio to its intensity, until function ceases entirely. If recovery takes place, the stage of hypersensitiveness is again passed through before the kidney returns to normal in its function. That water may be excreted in this manner was proved to the satisfaction of these investigators; sodium chlorid, though not so thoroughly investigated, appeared to follow the same course. Pohl's[14] previous efforts resulted in somewhat similar conclusions regarding the excretion of salt and nitrogen.

These theories seem to indicate that the kidney plays an active part in the excretion of excess water, salt, nitrogen or other substances. Another conception that might explain the phenomenon under consideration is that the augmented production of urinary constituents may be passive rather than active. Barcroft and Straub[16] showed how diuresis could, under certain physiologic conditions, occur without the consumption of oxygen, that is, an increased production of urine occurred with a passive kidney, presumably by a process of filtration. The constant presence of glucose in the urine in experimental uranium nephritis (Table 2, Dog 23; Table 3, Dog 10; Table 4, Dog 15; Table 11, Dog 27, and Table 14; Dog 1), which is due to a renal glycosuria,[17] points toward the possibility that such a kidney may be superpermeable to other substances besides sugar.

These two factors, "hypersensitiveness" and increased permeability may play a secondary rôle in producing the excess of urinary nitrogen found in these experimental animals and possibly in human beings. The primary cause is, in all probability, to be sought in an increased protein catabolism, an excess of waste nitrogen in the blood being presented to the kidney for excretion.

15. Schlayer: Beiheft. z. med. Klin., Part 9, 1912, viii, 211, gives a summary of these views.

16. Barcroft and Straub: Jour. Physiol., 1910, xli, 145.

17. Frank: Arch. f. exper. u. Pharmakol., 1913, lxxii, 387.

2. *Increased Protein Catabolism.*—In order to determine whether increased protein catabolism was a cause for the negative balances in experimental uranium nephritis, recourse was had to two procedures: (1) determining the sulphur in the urine; (2) estimating the non-protein nitrogen of the blood.

TABLE 5.—NITROGEN, SULPHUR AND RATIO OF NITROGEN TO—

Dog No.	23			25		
Diet	Constant containing meat, lard, cracker dust, bone ash and water.			Constant amounts of meat, lard, cracker dust and bone ash. Amounts of water varied.		
Urinary Nitrogen and Sulphur, gm.	N	S	N : S	N	S	N : S
Average of control days.....	2.91	0.14	21 : 1	8.54	0.49	17 : 1
Days of Test						
First	3.34	0.16	21 : 1	6.21	0.52	12 : 1
Second	3.20	0.21 †	16 : 1	....	....	....
Third	3.58	0.28 †	13 : 1	6.31	0.42	15 : 1
Fourth	4.34	0.27 †	16 : 1	6.21	0.44	14 : 1
Fifth	4.36	0.26 †	17 : 1	....	....	....
Sixth	.....	.....	.....	4.32	0.30	14 : 1
Seventh	.....	.....	.....	.....	.....	.....
Eighth	.....	.....	.....	.....	.....	.....
Ninth	.....	.....	.....	.....	.....	.....
Tenth	.....	.....	.....	.....	.....	.....
Eleventh	.....	.....	.....	.....	.....	.....
Twelfth	.....	.....	.....	.....	.....	.....
Thirteenth	.....	.....	.....	.....	.....	.....
Fourteenth	.....	.....	.....	.....	.....	.....
Fifteenth	.....	.....	.....	.....	.....	.....
Sixteenth	.....	.....	.....	.....	.....	.....
Seventeenth	.....	.....	.....	.....	.....	.....
Eighteenth	.....	.....	.....	.....	.....	.....
Nineteenth	.....	.....	.....	.....	.....	.....
Twentieth	.....	.....	.....	.....	.....	.....
Approximate results of observations on: N		+			—	
Approximate results of observations on: N : S		—			—	
Approximate results of observations on: S		+			=	

† This indicates that the injection of uranium nitrate was repeated.

1. The N : S Ratio: As the result of protein catabolism in the organism there should be an increase in urinary sulphur as well as nitrogen. The N : S ratio should theoretically remain constant. Table 5

summarizes the studies made in this connection. They give no clear-cut results. There are certain evident objections to drawing conclusions concerning the constancy of protein catabolism from the N : S ratio. In the first place a nephritic kidney may be able to eliminate nitrogen readily and retain sulphur, or vice versa (as in Dog 25). In

—Sulphur in the Urine of Dogs in Experimental Uranium Nephritis

10			22			24			27		
Constant containing meat, lard, cracker dust, bone ash and water.			Constant containing meat, lard, cracker dust, bone ash and water.			Constant amounts of meat, lard, cracker dust and bone ash. Amounts of water varied.			Salt solution only. Given by stomach-tube.		
N	S	N : S	N	S	N : S	N	S	N : S	N	S	N : S
4.81	0.31	16 : 1	5.76	0.36	16 : 1	5.75	0.37	16 : 1	2.01	0.14	14 : 1
4.48	0.29	15 : 1	5.43	0.34†	16 : 1	5.76	0.40	15 : 1	2.72	0.24	12 : 1
4.73	0.32	15 : 1	5.38	0.34	16 : 1	4.99	0.38	13 : 1	2.68	0.19	14 : 1
4.69	0.34	14 : 1	4.80	0.33	15 : 1	5.69	0.39†	15 : 1	2.33	0.16	14 : 1
4.28	0.31	14 : 1	4.83	0.40	12 : 1	5.98	0.38	16 : 1	1.65	0.11	15 : 1
4.42	0.31	14 : 1	5.10	0.33	15 : 1	6.51	0.39†	17 : 1	2.30	0.14	17 : 1
5.01	0.31	16 : 1	5.88	0.30	20 : 1	6.12	0.39	16 : 1	2.88	0.18	17 : 1
5.60	0.30	19 : 1	5.88	0.31	20 : 1	7.39	0.45†	16 : 1	2.82	0.19	15 : 1
5.98	0.29	20 : 1	....	....	.....	....	....	.....	3.05	0.18	17 : 1
6.96	0.33	21 : 1	....	....	.....	8.60	0.50	17 : 1	3.61	0.22	16 : 1
5.83	0.27	22 : 1	6.98	0.34	21 : 1	9.42	0.52	18 : 1			
5.88	0.26	22 : 1	5.52	0.34	17 : 1						
5.47	0.26	21 : 1	6.91	0.35	20 : 1						
4.64	0.23	20 : 1									
4.81	0.24	20 : 1									
5.69	0.33	17 : 1									
4.13	0.22	18 : 1									
4.68	0.26	18 : 1									
5.63	0.32	18 : 1									
4.99	0.28	18 : 1									
5.45	0.29	19 : 1									
	+			+			+			+	
	+			+			=			=	
	—			=			+			+	

‡ In this table + means increased; —, diminished; =, constant.

the second place, the various forms of protein destroyed probably contain different percentages in composition of nitrogen and sulphur, and thus do not present a constant ratio. This is especially true when

TABLE 6.—Result of Experiment with Dog 31 *

Period of Nephritis	Albumin per 1,000 by Esbach Test	Weight kilos	Volume of Urine c.c.	Urinary Nitrogen gm.	Water Balance c.c.	Nitrogen Balance gm. †	Non-Protein Nitrogen of Blood, mg. per 100 c.c.	Remarks
Days								
Control...	0.0	8.67	340	....	— 60	.....	21.6	
Control...	0.0	8.62	338	....	— 58	.....		
Control...	0.0	8.62	327	4.29	— 47	+ 1.24	21.8	
Control...	0.0	8.56	370	5.39	— 90	+ 0.14		
		8.56	345	5.43	— 65	+ 0.10	24.0	0.01 gm. uranium nitrate injected subcutaneously.
Control...	0.0							
Test								
1	1.0	8.44	415	4.84	—135	+ 0.69		
2	2.0	8.17	585	5.35	—305	+ 0.18	35.6	
3	2.0	7.86	630	6.82	—350	— 1.19	51.2	
4	1.7	7.47	640	6.21	—360	— 0.79	68.8	Vomited solid matter containing 0.11 gm. nitrogen.
5	1.5	....	174	1.28	.....	— 1.88	100.0	Ate only part of food. Food eaten contained 3.21 gm. of nitrogen. Vomitus contained 3.21 gm. of nitrogen.

* The daily diet of this animal consisted of chopped beef-heart, 160 gm.; cracker dust, 32 gm.; lard, 16 gm.; bone ash, 8 gm.; water, 280 c.c. This diet containing 6.13 gm. of nitrogen was fed for twelve days before specimens were collected for analysis. The dog was catheterized at the completion of each twenty-four-hour period.

† The amount of nitrogen estimated as being excreted in the feces daily was 0.6 gm.

the ratios of the control periods represent the excretory products of food proteins that have a widely different source from the dog's own tissues. In this connection the results in Dog *27* are significant, as this animal was given only salt and water and no protein food. In this experiment the N : S ratio remained constant, thus pointing toward an increased protein catabolism as the source of the excess of nitrogen eliminated. The results as a whole, however, are inconclusive; like many studies in nephritis they yield figures which are at times constant, at others variable, and it becomes necessary to look further for a more trustworthy evidence on the question in hand.

2. The non-protein nitrogen of the blood: An increase in the non-protein nitrogen of the blood has usually been considered due to retention by a diseased kidney, in both experimental and clinical studies. Thus in the researches of Folin, Karsner, Howard and Denis[18] such an increase found in uranium and cantharidin nephritis has been interpreted as a retention of nitrogen. In the present experiments a similar increase in the non-protein nitrogen of the blood was demonstrated, see Tables 6, *7*, 8 and 9. While this increase occurred in the blood, nitrogen was not diminished in the urine, but was excreted in quantities distinctly greater than that taken in in the food. This led to the inevitable conclusion that both the high blood and urinary figures for non-protein nitrogen were due not to kidney insufficiency, but to an increased protein catabolism.

The water metabolism in this connection demands some study. In the protocols of Tables 6 and *7* it is evident that the animals lost a considerable amount of water. This may have resulted in an inspissation of the blood and a consequent rise in the percentage of the non-protein nitrogen of the blood without an absolute increase. The high blood-figures obtained seem to contradict this possibility. Furthermore, as shown in Table 8 and very clearly in Table 9, when extra water was given by stomach-tube, a positive water balance was obtained, and yet the non-protein nitrogen of the blood was markedly higher than in the control periods, thus verifying the conclusions that an increased protein catabolism occurred. In both of these protocols, however, it is perfectly evident that when the water balances are again allowed to become negative the figures for non-protein nitrogen of the blood undergo a corresponding rise. That a water loss or gain to the body is a factor that influences the results in quantitative estimations of the non-protein nitrogen of the blood, becomes apparent.

Another problem presents itself for solution at this point: Why does a kidney retain some of this nitrogen and excrete the

18. Folin, Karsner, Howard and Denis: Jour. Exper. Med., 1912, xvi, 789.

TABLE 7.—Result of Experiment with Dog 33*

Period of Nephritis	Albumin by Esbach per 1,000 Test	Weight kilos	Water Intake c.c.	Volume of Urine c.c.	Urinary Nitrogen gm.	Nitrogen of Vomit gm.	Fecal Nitrogen gm.	Nitrogen Balance gm.	Nonprotein Nitrogen of Blood, mg. per 100 c.c.	Remarks.
Days										
Control...	0.0	....	350	495	....	....	....	.....	28.0	
Control...	0.0	9.93	350	460	4.85	.....	....	.....	....	
Control...	0.0	9.80	350	610	5.97	....	....	.....	....	
Control...	0.0	9.70	350	520	6.65	....	....	.....	22.2	
Control...	0.0	9.60	350	485	6.49	....	....	.....	....	
Control...	0.0	9.68	350	365	6.09	....	....	.....	....	
Control...	0.0	9.63	350	435	6.79	....	....	.....	....	
Control...	0.0	9.60	350	400	6.22	....	....	....	....	
Control...	0.0	9.59	350	395	6.34	....	....	....	....	
Control...	0.0	....	350	400	6.48	....	0.54	—0.98	25.1	
Control...	0.0	9.55	350	395	8.33	....	0.55	—2.84	....	
Control...	0.0	9.48	350	430	7.29	....	0.47	—1.72	....	0.014 gm. uranium nitrate injected subcutaneously.
Test										
1	0.2	9.42	850	930 ‖	7.58	....	....	—1.54	....	
2	1.8	9.17	1,850	1,170 ‖	5.51	1.44	1.31	—2.17	45.6	Diarrhea; vomit.
3	0.4	9.09	1,850	1,350	5.42	....	4.48‡	—3.86	56.2	Diarrhea; vomit.
4	0.2	9.08	1,850	1,650	6.94	....	7.62	—8.52	59.4	Diarrhea.
5	0.2	9.03	1,850	1,785	7.36	....	1.10	—2.42	63.2	
6	0.2	8.95	1,850	1,960	7.46	....	....	—1.42	62.5	
7	...	....	350	1,030	8.38	0.06	1.20	—3.60	49.5	Vomit.

* The daily diet of this animal consisted of chopped beef-heart, 150 gm.; cracker dust, 40 gm.; lard, 20 gm.; bone ash, 10 gm.; the water was varied in amount as indicated under water intake. This diet containing 6.04 gm. of nitrogen was fed for six days before specimens were collected for analysis. The dog was catheterized at the completion of each twenty-four-hour period.

† The water balance could not be calculated because of diarrhea. The figures for weight show that there was a considerable loss of water.

‡ Includes nitrogen of both vomit and feces.

‖ Contaminated with fecal matter.

remainder? Table 4 shows how an animal with a nephritis of considerable intensity can eliminate large amounts of nitrogen without any difficulty. It seems probable, therefore, that the augmented blood nitrogen resulting from protein catabolism, circulates in some abnormal chemical combination which the kidney is unable to excrete. When the disease has been in progress for about four days, this chemical compound may be changed into another, which readily passes through the kidney and causes the large negative nitrogen balances present from about this time on.

To make a practical clinical application of these phenomena, it is evident that in interpreting the significance of an increase of non-protein nitrogen in the blood in nephritis, the following facts must be taken into consideration:

1. Retention of nitrogen by an insufficient kidney.
2. Inspissation of the blood due to loss of water.
3. Increase of protein catabolism.
4. The chemical combination in which the non-protein nitrogen exists in the blood.

The cause for the increased protein catabolism may lie in the fact that uranium may entail pathological changes involving other organs than the kidney. In this respect uranium nephritis in dogs has very suggestive relations to human nephritis. The loss of glucose is too slight to have a far-reaching influence on protein metabolism. Thus the D : N ratio in Table 14, Dog 1, whose diet was carbohydrate-free, is very much below 1, indicating that only a very small fraction of the sugar circulating in the blood is excreted and that thus the loss of sugar with its protein-sparing influence cannot be called to account for all the increased protein catabolism.

NITROGEN EXCRETED IN THE SUCCUS ENTERICUS

With the nitrogen content of the feces unchanged from the normal, that of the urine increased, and the non-protein nitrogen of the blood considerably raised, it is of interest to note what effect these apparently contradictory changes in uranium nephritis may have on certain other phases of the nitrogen metabolism. This was studied for the succus entericus in dogs from which the intestinal secretion was collected by means of a Thiery fistula. For the technic of these operations, the methods of calculation, etc., the reader is referred to a previous paper[19] in which the control periods of these animals were discussed. At that time the following conclusion was reached: nitrogen equivalent to about 35 per cent. of the nitrogen intake, though not necessarily derived directly from it, is daily secreted in the succus entericus of dogs

19. Mosenthal, Herman O.: Jour. Exper. Med., 1911, xiii, 319.

on a mixed diet; about 10 per cent. is excreted in the feces and about 25 per cent. is reabsorbed. It is clear from the protocols given in Table 10 that during the nephritic period the nitrogen content of the succus entericus tended to diminish. What effect such a diversion of nitrogen from its normal path of intermediary metabolism may have on the body's health must at present remain purely conjectural. We are led, however, to speculate on the possibility that the cause of some

TABLE 8.—RESULT OF—

Period of Nephritis	Albumin per 1,000 by Esbach Test	Weight kilos	Water Intake c.c.	Volume of Urine c.c.	Nitrogen Intake gm.	Urinary Nitrogen gm.
Days						
Control...	...	.....	655	...	9.91	....
Control...	...	17.62	655	735	9.91	....
Control...	0.0	17.60	655	740	9.91	....
Control...	0.0	17.61	655	700	9.91	8.76
Control...	0.0	17.65	655	680	9.91	9.07
Control...	0.0	17.63	655	720	9.91	8.77
Control...	0.0	17.68	655	700	9.91	8.52
Control...	0.0	17.64	655	740	9.91	8.89
Test						
1	0.0	17.57	2,655	2,800	9.91	8.25
2	1.0	17.42	3,055	3,220	9.91	8.59
3	0.5	17.53	3,855	3,710	9.91	9.90
4	Trace	18.14	3,155	2,500	9.91	8.20
5	0.2	18.00	1,500	1,565	‡0.0	4.44
6	0.5	16.83	0	960	‡0.0	3.58
7	0.2	15.98	0	640	‡0.0	4.20
8	0.2	15.76	800	780	‡0.0	5.16
9	Trace	15.70	800	640	‡0.0	3.59

* The daily diet of this animal consisted of chopped beef-heart, 270 gm.; cracker was varied in amount as indicated under water intake. This diet containing 9.91 gm. The dog was catheterized at the completion of each twenty-four-hour period.
‖ Ditto marks in this column indicate determinations on composite specimens.

symptom-complexes, such as uremia, may lie in the many intermediary cycles of metabolism, even when the urinary excretions are seemingly adequate. It is also apparent that the intestines do not supplement the functions of the kidney through vicarious excretion, simply because there is an abnormally large quantity of nitrogen to be eliminated; exactly what factors are involved in producing a diarrhea (see Table 7) and increased fecal nitrogen in certain instances and not in others, is not clear.

THE PARALLELISM OF NITROGEN WITH OTHER URINARY CONSTITUENTS

It has long been acknowledged that a nephritic kidney will retain certain substances while others may be normally excreted. This is also the case in uranium nephritis. Such a lack of parallelism has been noted in the preceding pages as existing between sulphur and nitrogen (Table 5) and between water and nitrogen (Table 1, Dog. 25).

—EXPERIMENT WITH DOG 35 *

Fecal Nitrogen gm. ‖	Water Balance c.c.	Nitrogen Balance gm.	Nonprotein Nitrogen of Blood, mg. per 100 c.c.	Remarks
....	.....	.....	31.7	Seventh day after feeding was begun.
....	— 80	.....	30.1	Twenty-fourth day after feeding was begun.
....	— 85	.....	....	
1.02	— 45	+ 0.13	....	
"	— 25	— 0.18	....	
"	— 65	+ 0.12	....	
"	— 45	+ 0.37	....	
"	— 85	± 0.00	....	0.02 gm. uranium nitrate injected subcutaneously.
0.56	— 145	+ 1.10	....	
1.11	— 145	+ 0.20		
0.91	+ 145	— 0.90	47.8	
1.02	+ 655	+ 0.69	63.8	
0.61	— 65	— 5.05	69.4	
0.86	— 960	— 4.44	85.4	
0.23	— 640	— 4.43	88.9	
0.00	+ 20	— 5.16	....	
0.55	+ 160	— 4.13	82.7	

dust, 72 gm.; lard, 54 gm.; bone ash, 18 gm.; sodium chlorid, 2.5 gm. The water of nitrogen was fed for twenty-five days before the collection of urine was begun.
† Trace. ‡ Refused food.

Although several animals were studied very closely in this connection, the protocol of only one is reproduced here (Table 11, Dog 27). All yielded similar results. The nitrogen and sulphur in this case are both excreted in increased amounts during the nephritic period, so that the N : S ratio remains fairly constant (Table 5, Dog 27). While we have an excessive excretion of these two substances, sodium chlorid and the phosphates are retained; the power to excrete the former being recovered distinctly sooner. The same discrepancy between nitrogen and sodium chlorid elimination is seen in Table 2, Dog 23. Another inter-

TABLE 9.—Result of Experiment with Dog 34*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Weight kilos	Water Intake c.c.	Volume of Urine c.c.	Urinary Nitrogen gm.	Nitrogen of Vomit gm.	Fecal Nitrogen gm.	Water Balance c.c.	Nitrogen Balance gm.	Non-protein Nitrogen of Blood mg. per 100 c.c.
Days										
Control...	0.0	12.25	475	490	....	....	....	.....	.....	35.3
Control...	0.0	12.28	475	470	....	....	....	.....	.....	....
Control...	0.0	12.22	475	505	....	....	‡			
Control...	0.0	12.23	475	465	....	....	....	.....	.....	....
Control...	0.0	12.31	475	480	....	....	....	.....	.....	33.7
Control...	0.0	12.21	475	560	....	....	....	.....	.....	....
Control...	0.0	12.26	475	470	6.47	....	0.62	+ 5.	—0.12	....
Control...	0.0	12.22	475	485	5.91	....	"	— 10	+0.44	....
Control...	0.0	12.29	475	470	6.36	....	"	+ 5	—0.01	....
Control...	0.0	12.23	475	490	6.50	....	"	— 15	—0.15	....
Test §										
1	0.3	12.13	975	1,050	6.57	....	0.56	— 75	—0.16	....
2	0.4	12.10	1,975	1,970	6.44	....	0.69	+ 5	—0.16	40.9
3	0.2	12.46	2,375	2,020	6.38	....	0.55	+355	+0.04	61.3
4	Trace	12.54	2,375	2,165	6.59	....	"	+210	—0.17	66.5
5	Trace	12.64	2,525	2,430	7.60	....	"	+ 95	—1.18	56.8
6	0.2	12.34	2,525	2,690	8.19	....	0.59	—165	—1.81	41.5
7	0.5	11.48	475	1,090	6.39	....	0.56	—615	+0.02	63.8
8	0.5	11.17	475	830	8.29	....	0.59	—355	—1.91	77.4
9	...	10.83	475	720	8.61	0.70	"	—245	—2.93	75.6

* The daily diet of this animal consisted of chopped beef-heart, 195 gm.; cracker dust, 52 gm.; lard, 24 gm.; bone ash, 13 gm.; sodium chlorid, 2 gm.; the water was varied in amount as indicated under water intake. This diet, containing 6.97 gm. of nitrogen, was fed for nine days before the collection of urine was begun. The dog was catheterized at the completion of each twenty-four-hour period.

‡ The ditto marks in this column indicate determinations on composite specimens.

§ At this point 0.015 gm. uranium nitrate was injected subcutaneously.

TABLE 10.—Nitrogen of the Urine, Feces and Succus Entricus of Two Days with Experimental Uranium Nephritis.*

TABLE 10.—Nitrogen of the Urine, Feces and Succus Entricus of Two Days with Experimental Uranium Nephritis*

Dog No.	Period of Nephritis	Albumin per 1,000 by Esbach Test	Nitrogen for twenty-four hours, gm.						Remarks
			Intake	Urine ‡	Feces ‡	Succus Entericus	Balance of Nitrogen †		
							Urinary	Succus Entericus	
5	Control...	0.0	7.35	5.81	0.73	2.99			
	Control...	0.0	7.35	"	"				
	Control...	0.0	7.35	"	"	1.59			
	Control...	0.0	7.35	"	"	1.34			
	Control...	0.0	7.35	"	"				
	Days								
	1	0.8	7.35	5.96	0.61	0.64	—0.15	+1.33	0.01 gm. uranium nitrate injected subcutaneously.
	2	2.0	7.35	5.45	"	0.96	+0.36	+1.01	
	3	3.0	7.35	9.17	"	0.99	—3.36	+0.98	
	4	2.0	7.35	6.32	"	0.31	—0.51	+1.66	
	5	...	7.35	....	"	0.83	.....	+1.14	Vomited.
	6	...	0.00	....	0.74	0.28	.....	+1.69	Fed water only.
	7	0.5	7.35	....	"				
	8	0.5	7.35	....	"	0.90	.....	+1.07	
	9	0.3	7.35	7.51	"	0.47	—1.70	+1.50	
	10	0.3	0.00	6.65	0.47	....	—0.84	.....	Refused to eat or drink.
7	Control...	0.0	4.33	3.44	0.31	1.80			
	Control...	0.0	4.33	2.93	"	1.23			
	Control...	0.0	4.33	"	"	1.06			
	Control...	0.0	4.33	"	"	0.94			
	Control...	0.0	4.33	"	"	1.00			
	Days								
	1	0.5	4.33	3.19	0.30	0.86	—0.16	+0.35	0.01 gm. uranium nitrate injected subcutaneously.
	2	4.0	4.33	3.29	"	0.52	—0.26	+0.69	
	3	4.5	4.33	3.30	"	0.47	—0.27	+0.74	
	4	4.5	4.33	3.31	"	0.58	—0.28	+0.63	
	5	5.0	4.33	3.61	"	1.04	—0.58	+0.17	
	6	5.5	4.33	3.85	"	0.84	—0.82	+0.37	
	7	2.0	4.33	2.80	"	1.01	+0.23	+0.20	
	8	2.5	4.33	....	"	1.63	.....	—0.42	Vomited.
	9	0.8	4.33	4.55	"	2.49	—1.52	—1.28	
	10	0.5	4.33	3.45	"	0.98	—0.42	+0.23	
	11	1.5	4.33	3.35	"	0.46	—0.32	+0.75	

* Both animals were kept on a constant diet of weighed amounts of hashed lean beef, lard, cracker dust and bone ash and measured quantities of water. Dog 5 was kept on such a diet ten days, Dog 7, seven days, before specimens were collected for analysis.
† As compared to average of observations in control period. ‡ Ditto marks indicate analysis of composite specimens.

TABLE 11.—Result of Experiment on Dog 27*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Volume Urine c.c.	Glucose		Urinary Nitrogen gm.	Urinary Sulphur gm.	Urinary Sodium Chlorid gm.	Urinary Phosphates gm.	Remarks
			Pct.	Gm.					
Days									
Control...	0.0	325	0.0	0.0	1.91	0.15	1.64	0.53	
Control...	0.0	390	0.0	0.0	1.99	0.14	....	0.55	
Control...	0.0	330	0.0	0.0	2.14	0.14	1.55	0.55	0.02 gm. uranium nitrate injected subcutaneously.
Test									
1	1.0	515	0.7	3.6	2.72	0.24	1.60	0.84	
2	2.0	300	2.0	6.0	2.68	0.19	0.88	0.77	
3	1.0	495	0.7	3.5	2.33	0.16	0.39	0.37	
4	0.5	250	0.6	1.5	1.65	0.11	0.73	0.20	Vomited 95 c.c. of fluid.
5	0.5	290	0.7	2.0	2.30	0.14	0.54	0.24	
6	0.5	320	0.9	2.9	2.88	0.18	0.94	0.31	Vomited 55 c.c. of fluid.
7	0.5	415	0.6	2.5	2.82	0.19	1.21	0.20	
8	0.5	440	0.6	2.6	3.06	0.18	2.53	0.29	
9	0.7	530	0.7	3.7	3.61	0.22	3.24	0.32	

* This animal was given water and 1.6 gm. of sodium chlorid daily. The dog was catheterized at the completion of each twenty-four-hour period.

esting example of this lack of parallelism occurs when, with an excessive total nitrogen excretion, there is a retention of uric acid, one of the constituent nitrogenous substances, as shown in Table 14, Dog 1. Kraus[5] demonstrated an increase of uric acid excretion in dogs with uranium nephritis. In view of the variation found in the elimination of urinary nitrogen it would seem not at all improbable that both conditions, an increased, as well as a diminished uric acid excretion, might be found in cases of uranium nephritis of varying intensity. From the discussion as to the cause of extrarenal nitrogenous metabolism it

TABLE 12.—Blood-Pressure Readings in Millimeters of Mercury on Dog 1

	No. of Readings	Maximum	Minimum	Average
Before injection of uranium nitrate, thirteen days	3	90	85	88
During period of albuminuria, following the injection subcutaneously of 0.015 gm. uranium nitrate, seven days	7	130	95	117
Subsequent period, six days	4	100	90	96
During period of albuminuria, following a second subcutaneous injection of 0.015 gm. of uranium nitrate, four days	4	120	105	113
Subsequent period, twenty-nine days	8	110	105	107
During period of albuminuria, following a third subcutaneous injection of uranium nitrate; 0.02 gm. injected, fifteen days	12	140	105	122
Subsequent period, twenty-three days	11	120	100	113
During period of albuminuria, following a fourth subcutaneous injection of uranium nitrate; 0.02 gm. injected, seven days	6	135	120	125

becomes clear that, while many of the instances of lack of parallelism in the excretion of urinary elements may be ascribed definitely to the local lesions in the kidney, there are others that are dependent on remote metabolism changes.

INCREASE OF BLOOD-PRESSURE IN URANIUM NEPHRITIS

The blood-pressure was determined by a modified Riva-Rocci method devised by Janeway.[20] It was extensively studied on two dogs, Dog 1, Table 12; Dog 8, Table 13, and for shorter periods on others.

20. Janeway: Proc. Soc. Exper. Biol. and Med., 1909, vi, 108.

Both tables show a rise of blood-pressure which is most marked during the periods of uranium nephritis, but which does not return completely to normal when the albuminuria has ceased. In this way a distinct permanent rise of blood-pressure was obtained in one animal after three nephritic periods, in the other after seven. Concomitant determinations of urinary nitrogen, uric acid and blood-pressure followed for thirty-two days. Table 14, Dog 1 shows that the blood-pressure was maintained at its greatest height while there was an increased protein catabolism as indicated by the increased amounts of nitrogen in the urine, and also a persistent retention of uric acid. It is probable that the increased protein catabolism and the rise of blood-pressure are in some way related, and that the disturbance leaves some per-

TABLE 13.—Blood-Pressure Readings in Millimeters of Mercury on Dog 8

Date 1910	Gm. of Uranium Nitrate Injected Subcutaneously	No. of Readings	Maximum	Minimum	Average
7/24-8/8	(Control Period)	8	100	85	91
7/12	0.01				
10/4	.....	1	90	90	90
10/18	0.01				
10/31	.....	1	105	105	105
11/17	0.015	1	105	105	105
12/2	.....	1	110	110	110
1911					
3/8-3/15	.....	3	120	110	115
3/15	0.015				
4/ 5-4/7	.....	3	120	115	117
7/15-7/17	.....	3	115	110	112
7/19	0.015				
9/19	0.015				
11/3	0.015				
11/3-11/26	.....	4	125	115	119

manent impairment of the organism, is indicated by the fact that the blood-pressure remains high even though the nitrogen of the urine returns to its normal level. The kidneys of these two animals did not show the changes of chronic nephritis, on gross inspection or on microscopic examination. Dog 8 showed a very few small areas of round-cell infiltration, such as might very well have been present in any animals that had not been subject to repeated attacks of nephritis; in Dog 1 only the changes of an acute uranium nephritis were found, the animal being killed seven days after the last injection.

CONCLUSIONS

In experimental uranium nephritis, nitrogen excretion may be increased or diminished in amount; an increased elimination is due

TABLE 14.—Result of Experiment on Dog 1*

Period of Nephritis	Albumin per 1,000 by Esbach Test	Weight kilos	Volume of Urine c.c.	Glucose		Urinary Nitrogen gm.	Urinary Uric Acid gm.	Blood-Pressure mm. of Mercury
				Pct.	Gm.			
Average of three control days †	0.0	10.64	365	0.0	0.0	9.24	0.07	108
Test								
1	0.1	10.42	635	0.1	0.6	12.42	0.13	105
2	0.2	10.52	295	0.2	0.6	5.36	0.05	110
3	1.0	10.22	700	1.0	7.0	13.30	0.03	110
4	1.3	10.13	510	1.3	6.6	10.26	0.02	
5	1.9	9.85	685	1.9	13.0	14.74	0.03	125
6	1.5	9.76	535	1.5	8.0	12.11	0.02	135
7	1.3	9.61	520	1.3	6.8	12.20	0.02	140
8	1.0	9.63	480	1.0	4.8	10.06	0.02	125
9	1.2	9.55	620	1.2	7.4	12.30	0.02	125
10	1.8	9.37	590	1.8	10.6	12.61	0.02	120
11	0.8	9.38	420	0.8	3.3	11.04	0.01	120
12	0.5	9.53	305	0.5	1.5	8.44	0.01	125
13	0.3	9.65	315	0.3	0.9	11.03	0.04	120
14	0.1	9.62	410	0.1	0.4	10.14	0.05	
15	0.0	9.74	270	0.0	0.0	6.26	0.06	115
16	0.0	9.75	360	0.0	0.0	7.95	0.06	100
17	0.0	9.77	295	0.0	0.0	‡ 8.99	‡ 0.07	
18	0.0	9.73	390	0.0	0.0	"	"	
19	0.0	9.74	305	0.0	0.0	7.19	0.06	105
20	0.0	9.65	280	0.0	0.0	"	"	
21	0.0	9.80	215	0.0	0.0	8.80	0.07	
22	0.0	9.72	385	0.0	0.0	"	"	105
23	0.0	....	255	0.0	0.0	6.95	0.06	115
24	0.0	9.75	285	0.0	0.0	"	"	115
25	0.0	....	265	0.0	0.0	8.69	0.11	115
26	0.0	....	290	0.0	0.0	"	"	
27	0.0	9.73	205	0.0	0.0	9.80	0.10	120
28	0.0	9.76	300	0.0	0.0	"	"	
29	0.0	....	310	0.0	0.0	8.00	0.08	115
30	0.0	9.78	160	0.0	0.0	"	"	
31	0.0	....	280	0.0	0.0	9.19	0.09	115
32	0.0	9.80	275	0.0	0.0	"	"	

* The daily diet of this animal consisted of hashed lean beef, 250 gm.; lard, 50 gm.; bone ash, 15 gm.; water, 400 c.c. This diet was fed for twenty-one days before specimens were collected for analysis.

† At this point 0.02 gm. uranium was injected subcutaneously.

‡ From this point on the ditto marks indicate that the urine analyses were performed on a specimen collected in an interval of forty-eight hours instead of during twenty-four as previously.

not to any previous retention, but to an augmented protein catabolism, a diminished excretion to kidney insufficiency.

The laws governing the elimination of nitrogen in the urine in nephritis are not haphazard or "bizarre," but such other factors as food intake, normal stools, etc., being constant, depend largely on three conditions: the degree of protein catabolism, the chemical combination in which the non-protein nitrogen exists in the blood and the permeability of the kidney.

The normal nitrogen content of the feces, except during the rare occurrences of diarrhea, the diminished amount of nitrogen in the succus entericus, the increase in the non-protein constituents of the blood, the lack of parallelism between nitrogen and other urinary constituents, and the increased blood-pressure, make it clear that in uranium nephritis we have a disease which implicates the organism as a whole and not the kidneys alone; furthermore, that the various functions of the body do not necessarily supplement each other by vicarious excretion, etc., as is often assumed, but that each one to a great extent follows its own independent laws. Human nephritis presents such a many-sided picture that it seems probable that many of the facts worked out for experimental uranium nephritis are applicable to it. The only claim that can be made for them at present, however, is that they be considered as suggestions on which to base further observations.

In the interpretation of an increased non-protein nitrogen of the blood in nephritis, four factors are to be considered: (1) retention of nitrogen by an insufficient kidney; (2) inspissation of the blood, due to loss of water; (3) increase of protein catabolism; (4) the chemical combination in which non-protein nitrogen exists in the blood. Hitherto general attention has been paid only to the first of these.

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FAMILY PERIODIC PARALYSIS

REPORT OF A TYPICAL CASE, WITH METABOLISM STUDY *

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This is a curious and rare disease of which we have as yet only a few reports in the literature, most of which have been from this country. The first report appears to have been that of Westphal[1] in 1885. Cousot reports five cases, Goldflam[2] nineteen and Taylor eleven cases. Taylor,[3] in his exhaustive paper published in 1898, collected at that time fifty-three cases. Since then a few other cases have been reported, three by J. K. Mitchell, Flexner and Edsall.[4] Last year Gardner[5] reported a single isolated case which he studied in an interesting way. Dr. L. Pierce Clark[6] last year reported a new subtype of this palsy. The most important and extensive observations, however, have been made by Dr. G. E. Holtzapple,[7] a general practitioner of York, Pa., and despite the subsequent reports, Holtzapple's paper still constitutes the most important contribution to the subject. His paper is based on observations running over a period of twenty-two years made on one family in four generations. In this family he has observed seventeen cases of family periodic paralysis, eighteen cases of sick headache and five cases of paralysis and headache. Fourteen members of this family have had paralysis only and thirteen have had attacks of headache only. The total number afflicted with

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* From the Wards of the Allegheny General Hospital and the Laboratory of Dr. J. P. McKelvy, Pittsburgh.

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2. Goldflam, S.: Ueber eine eigenthumliche Form von periodischer, familiarer wahrscheinlich autointoxicatorische Paralyse, Ztschr. f. klin. Med., 1891, xix, Supplement, 240; Weitere Mittheilung über die paroxysmale, familiare Lähmung, Deutsch. Ztschr. f. Nervenh., 1896, vii, 1; ibid., 1897, xi, 242.

3. Taylor, E. W.: Family Periodic Paralysis, Jour. Nerv. Ment. Dis., 1898, xxv, 637 and 719.

4. Mitchell, Flexner and Edsall: Brain, 1902, xxv, 109.

5. Gardner, H. W.: A Case of Periodic Paralysis, Brain, 1913, xxxv, 243.

6. Clark, L. Pierce: Remarks upon the Irregular and Unusual Types of Familial Periodic Paralysis and Conditions Simulating the Same with a Preliminary Report upon a New Subtype of this Palsy, Review of Neurology and Psychiatry, 1913.

7. Holtzapple, G. E.: Periodic Paralysis, Jour. Am. Med. Assn., 1905, xlv, 1224.

either paralysis or headache was thirty-two. Of the seventeen members who have suffered from attacks of periodic paralysis, ten were still living at the time of Holtzapple's report. Six of the seven who died succumbed in an attack of paralysis, one of them in Holtzapple's presence. Of this paralytic group, fourteen were under his personal observation. The disease was transmitted through the father in six instances and through the mother in four instances; through the father having had attacks of sick headache only in four instances and through the mother having had attacks of sick headache only in three instances. In nine cases the disease was transmitted through the father, and eight through the mother. Holtzapple describes the attacks as follows:

> This affection in its typical form is characterized by periodic flaccid motor paralysis, involving all of the voluntary muscles, except those of the face, eyes, tongue, organs of speech, of deglutition and the sphincters of rectum and bladder. The attacks may be distinctly periodic for a time and at short intervals, especially in young adults, but frequently later in life at much longer and irregular intervals. The paralysis may be partial or complete, localized or general; the upper extremities alone or only the lower may be involved. It may be confined to the neck, or one-half of the body may be completely paralyzed, while partial paralysis affects the other half. The paralysis may be partial in the morning and become complete during the day.
>
> During an attack of paralysis there may be one or more periods of marked improvement, usually of a few hours' duration, followed by complete helplessness. In a typical attack of complete general paralysis the patient is utterly helpless, cannot move a finger or toe, can neither lift nor turn the head on the pillow, and if unsupported, the head either drops on the sternum or backward between the scapulae. In some instances breathing becomes distinctly labored, and deep breathing, coughing and vomiting impossible. Speech and deglutition are in rare instances affected. The order of involvement is not always the same. It most frequently begins in the muscles of the lower extremities, but may only involve those of the upper or the muscles of the neck. There are no sensory symptoms, except in some instances formication and numbness in the paralyzed parts, also a sense of heaviness and a tired feeling, which at times become very annoying to the patient, necessitating frequent change of posture, to the great relief of the patient.

Holtzapple states that "the duration of an attack may be a few hours, one, two or in rare instances, three full days." Recovery may be rapid, or it may require three or four hours or even half a day. "It is nothing uncommon for one of these patients to be as helpless as a log at 7 a. m. and at 11 a. m. be engaged in doing a hard day's work, not feeling the slightest inconvenience from having been completely paralyzed a few hours before."

The frequency of attacks varies greatly in different members of the family and also in the same individual at different periods. Attacks are most frequent between puberty and the middle period of life; later they become less frequent and more irregular. During an attack the mind remains perfectly clear. Neither cranial nerves nor special senses are involved and the patient retains full control of bladder and rectum.

During severe attacks the pulse is weak and irregular and there is evident cardiac dilatation. During the intervals between attacks the members of the family seem perfectly well.

The hereditary nature of the attacks seems thoroughly established inasmuch as every one of those paralyzed had either a father or mother who was subject to either similar paralytic attacks or sick headache or both. The headache attacks are very similar to those of ordinary hemicrania.

Holtzapple studied 139 specimens of urine, seventy-three specimens from six members of the paralytic group, thirty-six specimens from three individuals who have characteristic headache and thirty specimens from persons who were the picture of health. He found that the members of the paralytic group were not excreting normal quantities of metabolic products. In all of Holtzapple's cases an attack was brought on by overeating.

The case which Gardner reported appears to be a perfectly typical one, although there is no history of heredity in the family. He believes that the disease is due to a congenital defect of metabolism. Dr. Head offered the suggestion to Dr. Gardner that the disease might be an expression of anaphylactic reaction to some form of food such as pork. And although it was known that attacks have occasionally followed the eating of pork sausage, Gardner did not feel justified in making this experiment in his case, as, if the theory were true, the experiment would not be without danger.

Gardner summed up his reasons for believing the attacks due to presence of toxins because of some defect in metabolism as follows:

1. The many points of resemblance to other conditions which are undoubtedly due to auto-intoxication.

2. The sudden onset and the rapid recovery.

3. The invariable occurrence of the phenomena after sleep, when waste and toxic products may be assumed to accumulate, just at the time that intestinal digestion is taking place.

4. The fact that the condition might occasionally be walked off.

5. The symmetrical distribution of the paralysis.

6. The occurrence of headache, drowsiness, thirst, anorexia, aching of the limbs and sweating during the attacks. These toxic symptoms closely resemble those which obtain in other transitory toxemias.

7. The fact that previous attacks of headache, in all probability toxemic, had been replaced by the attacks of paralysis.

8. The high specific gravity of the urine passed during the attacks, and the presence in it of small quantities of indican.

9. The presence of high pulse tension with accentuated aortic second sound and slow pulse in the initial stages and the cardiac dilatation which so rapidly followed.

And acting on this theory he prescribed for his patient as follows:

1. The patient was to give up drinking beer altogether, and to avoid all rich food; and he was to drink large quantities of water.

2. To take magnesium sulphate, 1 dram, in half a pint of hot water on rising every morning.

3. To take compound pill of mercurous chlorid, 2 grains, once a fortnight at bedtime, fellowed by Epsom salts in the morning.

4. To take tincture of digitalis, 4 minims; potassium acetate, 20 grains; syrup, ½ dram, and peppermint water, 1 dram, three times a day.

5. To take caffein citrate, 7½ grains; potassium bromid, 10 grains; diluted hydrobromic acid, 15 minims; syrup 1½ dram, and chloroform water, ½ dram, in a tumbler of water whenever any warning symptoms of an attack made their appearance.

He writes that the attacks which had been getting more and more frequent and threatening to incapacitate the patient at once ceased after the institution of this treatment.

The record of our own case may be inserted at this point:

History.—The patient is a healthy-looking man aged 21, single, habits good. He does not drink or use tobacco. He denies specific disease of any kind. Occupation, foreman in rubber works; he formerly worked at blacksmith's trade. He works ten hours a day. He drinks a glass of wine occasionally.

Patient's great grandmother and grandfather on his mother's side suffered from periodic paralysis, the latter dying of it. A second cousin on his mother's side (a man in middle life) suffered with this disease for many years and suffers from it now. In this cousin the disease was never as severe as in the patient and of late years has grown a good deal less severe.

The patient for the last seven years has been subject to periodic attacks of paralysis. These attacks are of irregular occurrence lasting from a half hour up to three or four days. Of the severe and more prolonged attacks he has had about three or four in a year. He experiences some kind of an attack two or three times every week. They always come on in the night. He wakens in the morning to find himself paralyzed in some part of his body; or he may waken in the night to find himself paralyzed. In severe attacks he is paralyzed in all parts of the body below the head (including the neck). The muscles of the face, tongue, eyes and throat have never been affected. He may recover within half an hour or an hour completely, even from a severe attack. During a severe attack he has only slight motion in the various members of his body. In lighter attacks he wakens in the morning to find some part of his body paralyzed. It may be one leg, or both legs, an arm or both arms, or an arm and leg on the same side or an arm on one side and a leg on the other. Neck muscles alone may be paralyzed. The legs are rather more commonly paralyzed than other parts of the body. In lesser attacks, when he wakens paralyzed, he goes about his work and gradually recovers—so gradually that he is not able to state just when improvement began; and usually about 8 or 9 o'clock in the morning he has entirely

recovered. Recalling some of the more severe attacks, he states that on the evenings preceding them he has always had a hearty meal and he attributes these attacks to the meals. He has never had pain or sensory symptoms of any kind. He has never seemed feverish or delirious, or in any way mentally upset.

The patient was admitted to the Allegheny General Hospital September 30, paralyzed all over his body, with only feeble movements in arms and legs. He was unable to raise his arms above his head, to stand or even turn in bed. This attack, which was a major one, had begun about sixty hours previously.

Examination.—Oct. 1, 1914, 2 p. m.: There is almost complete paralysis of the left arm. The right arm is paralyzed to a little less degree. There is but slight movement in legs. The patient is able to flex the feet, but not to extend them. The neck muscles are very weak. He is unable to raise the head from the bed and has only feeble power in throwing the head backward. The muscles of respiration are weak. The diaphragm is weak and he can protrude the abdomen only feebly. The knee-jerks are much reduced—quite feeble. Sensation as to temperature, pain and contact seem everywhere normal. The movements of the head and face all seem normal, also those of tongue and eyes. There is no defect of articulation, or in swallowing. There is no muscular atrophy. The patient's mind seems perfectly clear. The pulse is about 75; the blood-pressure seems somewhat reduced.

October 2, 2 p. m.: The nurse records that at 12 o'clock last night the patient seemed even weaker than in the afternoon and unable to turn himself in bed. Pulse about 50. When she observed him at 2 in the morning he seemed to have fully regained his strength.

The patient seems possessed of his normal strength of all parts of his body. He gives a firm grasp of the hand, and the legs are quite strong. There is no wasting of any of the muscles. The knee-jerks, which yesterday were very much reduced, are quite active to-day, forming a marked contrast to those of yesterday. Dr. Rosenbloom saw him, gave directions for food and diet and for examination of urine and feces. An attempted lumbar puncture was unsuccessful.

Observation at the Hospital.—Shortly after the patient was put to bed his pulse went down to 50 and continued low during the week he was in the hospital, ranging from 50 to 60. A day or two before leaving I joked with him, saying, "Why don't you get up an attack of paralysis, which you say you can do so readily?" His reply was, "You just give me a good, hearty meal to-night and I will guarantee to be paralyzed to-morrow morning."

It would seem that we need look for no further explanation of his freedom from attacks in the hospital than the diet which he took while there.

During his stay of one week in the hospital the patient seemed to be, after the first day, normal in every way. The blood-pressure was:

October 3: Systolic, 68; diastolic, 60.
October 4: Systolic, 68; diastolic, 55.
October 5: Systolic, 90; diastolic, 65.
October 7: Systolic, 92; diastolic, 72.
October 9: Systolic, 95; diastolic, 75.

From consideration of the review of the literature it will be noted that our own case is a highly typical one, and conforms in the main to the criteria laid down by Holtzapple. The attacks seem to be per-

fectly typical and much more frequent than in most of the cases reported; heredity is plain and clear. It is also like other cases in other respects as follows: The attacks always come on at night; they are often, if not always, preceded by a heavy meal; paralysis comes on during sleep; paralysis wears off by exercise; attacks last from a few hours to and never exceeding three days; there is absence of mental symptoms; there is absence of sensory symptoms; the paralysis is of flaccid character with absence of knee-jerks; the health of the patient between attacks is perfect. Our case also lends strong support to the views expressed by Gardner regarding the nature of the disease, namely, that it is probably due to some congenital defect of metabolism.

TABLE 1.—THE NITROGEN METABOLISM—

Day	Urine †								
	Volume c.c.	Nitrogen gm.	Urea-Nitrogen		Ammonia-Nitrogen		Creatinin ‡		
			Gm.	Per Cent. of Total Nitrogen	Gm.	Per Cent. of Total Nitrogen	Gm.	Nitrogen	Percentage of Total Nitrogen
1	1,300	14.9	12.6	84.6	0.51	3.4	0.75	0.275	1.8
2	2,125	15.2	12.9	84.5	0.55	3.6	0.86	0.314	2.06
3	1,200	15.4	13.1	85.1	0.62	4.0	0.97	0.354	2.3
4	1,550	15.5	13.0	83.9	0.64	4.1	0.70	0.256	1.7
5	1,420	15.8	13.3	84.1	0.75	4.8	0.86	0.314	2.0
6	1,400	15.1	12.9	85.4	0.66	4.6	0.67	0.244	1.6
7	1,240	15.2	13.3	87.5	0.72	4.7	0.78	0.285	1.9

* Creatin was absent from all specimen of urine.
† At no time did the urine contain acetone, diacetic acid, beta-oxybutyric acid, excess of
‡ Average creatinin coefficient = 4.8 mg. creatinin-nitrogen per kilogram of body weight.

Supporting this view are the facts that undoubtedly attacks have been produced (if not always) by hearty meals; and supported further by the fact that while in the hospital and on a limited diet the patient was free from attacks.

ABSTRACT OF METABOLISM STUDY BY DR. ROSENBLOOM

We have studied in this patient, in a seven-day metabolism experiment, the nitrogen metabolism and urinary nitrogen partition, the sulphur metabolism and urinary sulphur partition, the calcium, magnesium, phosphorus and fat metabolism. We have found a very low creatinin excretion and a very high "undetermined nitrogen" excretion; these findings may indicate the type of metabolic perversion which accounts for the paralytic seizure.

This condition has so many characteristics of a toxemia that it was thought that a complete metabolic study of this patient might throw some light on the disease. Some work has been carried out in the field already. Holtzapple found a marked diminution in the average quantity of urea eliminated by his paralytic group. As no attention was paid to diet and as the hypobromite method for the urea estimations was used, little reliance can be placed on this observation. Goldflam found that during the attacks the toxicity of the urine was increased as determined by Bouchard's method. This method has so many pitfalls that this result is of doubtful value. Singer and Goodbody[8] estimated the amounts of nitrogen, urea, uric acid, chlorids, total sulphates,

—AND URINARY NITROGEN PARTITION *

Urine †					Feces		Intake	Balance
Uric Acid			Undetermined Nitrogen		Nitrogen		Nitrogen	Nitrogen
Gm.	Nitrogen	Percentage of Total Nitrogen	Gm.	Pct. of Total Nitrogen	Gm.	Pct. of Nitrogen Intake	gm.	gm.
0.42	0.14	0.94	1.37	9.2	1.90	12.1	15.6	— 1.2
0.30	0.10	0.66	1.34	8.8	1.90	10.1	18.8	+ 1.7
0.36	0.12	0.78	1.21	7.9	1.90	11.8	16.2	— 1.1
0.39	0.13	0.84	1.47	9.5	1.90	11.6	16.4	— 1.0
0.36	0.12	0.76	1.32	8.4	1.57	9.4	16.7	— 0.67
0.33	0.13	0.86	1.17	7.7	1.57	9.3	16.9	+ 0.23
0.33	0.13	0.85	0.76	5.0	1.57	9.6	16.4	— 0.37

indican or any other abnormal constituent.

alkaline sulphates, ethereal sulphates and phosphates, in the urine of the case studied and found no marked changes in the amounts of these substances excreted. They did find a lessened amount of urine excreted during the attacks.

Crafts and Irwin[9] asserted that they had extracted from feces passed immediately after an attack, a substance which produced temporary paralysis when injected into guinea-pigs and rabbits. They also found that the amount of urea excreted during an attack appeared to be diminished. They also estimated in the urine the amounts of nitrogen, uric acid, chlorids, purin bases, alkaline and earthy phos-

8. Singer, H. D., and Goodbody, F. W.: A Case of Family Periodic Paralysis, with a Critical Digest of the Literature, Brain, 1901, xxiv, 257.

9. Crafts and Irwin: Am. Jour. Med. Sc., 1900, cxix, 651.

phates and preformed and ethereal sulphates without finding any marked changes. Their results as regards the isolation of a toxic substance from the feces could not be confirmed by Mitchell, Flexner and Edsall. The last-mentioned observers studied the amounts of ammonia and creatinin in the urine and seemed to think that there existed some relation between the attacks and the amount of creatinin excreted. They thought that the creatinin was an index of certain alterations in metabolism which leads up to a seizure and concluded that the attacks are due to some metabolic disturbance situated in the muscles.

TABLE 2.—THE SULPHUR METABOLISM—

Day	Sulphur gm.	Urine			
		Total Sulphate Sulphur		Inorganic Sulphate Sulphur	
		Gm.	Percentage of Total Sulphur	Gm.	Percentage of Total Sulphur
1	1.12	1.05	93.8	0.89	79.5
2	1.29	1.19	92.3	1.08	83.8
3	1.38	1.27	92.0	0.96	69.5
4	1.30	1.18	90.8	0.88	67.8
5	1.24	1.15	92.8	1.03	83.1
6	1.00	0.85	85.0	0.74	74.0
7	1.22	1.10	90.2	1.00	82.0

METABOLIC DATA

The patient was placed on Folin's[10] diet, consisting of:

Whole milk	500 c.c.
Cream	300 c.c.
Horlick's Malted Milk	200 gm.
Sugar	20 gm.
Salt	6 gm.
Eggs	450 gm.
Water	2,000 c.c.

This diet contains approximately 119 gm. of protein, 148 gm. of fat and 225 gm. of carbohydrate, yielding 2,787 calories, or about 46 calories per kilogram body weight of the patient.

Two ounces of the foregoing diet was taken out daily and the following constituents estimated: total nitrogen, phosphorus, sulphur, calcium and magnesium. The fat was estimated in a seven-day sample, 5 c.c. of each day's mixture being preserved by means of 2 drops of liquor formaldehydi.

10. Folin: Am. Jour. Physiol., 1905, xiii, 45.

A. *Method Used in Urine Analysis.*—The nitrogen was estimated according to Kjeldahl, the total sulphur by Benedict's[11] method. Total and ethereal sulphates by Folin's[12] method; the inorganic sulphates were computed by subtracting the ethereal sulphates from the total sulphates, and the neutral sulphur by subtracting the total sulphate sulphur from the total sulphur. Urea was estimated by Benedict's[13] method; ammonia by Folin's[14] method; total phosphorus by the Neumann[15] method, weighing the phosphorus as magnesium pyrophosphate; creatinin and creatin by Folin's[16] method; uric acid by Folin's[17]

—AND URINARY SULPHUR PARTITION

				Feces	Sulphur	
Ethereal Sulphate Sulphur		Neutral Sulphur		Sulphur	Intake	Balance
Gm.	Percentage of Total Sulphur	Gm.	Percentage of Total Sulphur	gm.	gm.	gm.
0.16	14.3	0.07	6.2	0.32	1.60	+ 0.16
0.11	8.5	0.10	7.7	0.32	1.70	+ 0.09
0.31	22.5	0.11	7.9	0.34	1.80	+ 0.08
0.30	23.0	0.12	9.2	0.34	1.50	— 0.14
0.12	9.7	0.09	7.3	0.30	1.40	— 0.14
0.11	11.0	0.15	15.0	0.30	1.30	0.0
0.10	8.2	0.12	9.9	0.30	1.32	— 0.22

method; calcium and magnesium by McCrudden's[18] method, and total acidity by Folin's[19] method.

B. *Methods Used in Analysis of Food.*—The nitrogen was estimated by the Kjeldahl method; total sulphur by the Wolf and Osterberg[20] modification of Benedict's method; calcium and magnesium by McCrudden's method after ashing and extracting the ash with hydro-

11. Benedict: Jour. Biol. Chem., 1909, vi, 363.
12. Folin: Am. Jour. Physiol., 1905, xiii, 51; Jour. Biol. Chem., 1906, 1, 131.
13. Benedict: Jour. Biol. Chem., 1911, viii, 405.
14. Folin: Ztschr. f. physiol. Chem., 1902, xxxvii, 161; Am. Jour. Physiol., 1903, viii, 330.
15. Neumann: Ztschr. f. physiol. Chem., 1902-1903, xxxvii, 129; 1904-1905, xliii, 35.
16. Folin: Am. Jour. Physiol., 1905, xiii, 45.
17. Folin: Ztschr. f. physiol. Chem., 1901, xxxii, 552.
18. McCrudden: Jour. Biol. Chem., 1911, x, 187.
19. Folin: Am. Jour. Physiol., 1903, p. 265.
20. Wolf and Osterberg: Biochem. Ztschr., 1910, xxix, 429.

chloric acid, and phosphorus by Neumann's method. Fat was estimated in a five-day period by Soxhlet extraction.

C. *Methods Used in Analysis of Feces.*—The feces were marked off by means of carmin into periods of four and three days, respectively. Nitrogen was estimated by the Kjeldahl method; sulphur by oxidizing with fuming nitric acid followed by Benedict's method; phosphorus by the Neumann method; calcium and magnesium by the same method as used for food, and fat by Soxhlet extraction.[21]

The accompanying tables contain the results obtained in this study.

COMMENT ON TABLE 1

In the seven-day metabolism period there was a loss of 5.81 gm. of nitrogen. The absorption of nitrogen is normal. The amount of nitrogen excreted as urea and uric acid is also normal. The creatinin nitrogen in gram and creatinin nitrogen in per cent. of the total nitro-

TABLE 3.—THE CALCIUM, MAGNESIUM—

Day	Urine			Feces		
	Phosphorus gm.	Calcium Oxid gm.	Magnesium Oxid gm.	Phosphorus gm.	Calcium Oxid gm.	Magnesium Oxid gm.
1	1.30	0.82	0.32	1.02	1.46	0.12
2	1.32	0.79	0.28	1.02	1.46	0.12
3	1.41	0.81	0.26	1.02	1.46	0.12
4	1.46	0.84	0.24	1.02	1.46	0.12
5	1.41	0.76	0.30	1.16	1.50	0.11
6	1.52	0.78	0.32	1.16	1.50	0.11
7	1.54	0.72	0.30	1.16	1.50	0.11

gen is markedly decreased as is also the creatinin coefficient. This may indicate a poor muscular efficiency of the individual, as it will be recalled that Shaffer finds the normal creatinin coefficient to be from 7 to 11 mg. of creatinin nitrogen per kilogram of body weight and thinks that it is an index of some special process of normal metabolism, taking place largely, if not wholly, in the muscles. On the other hand, it may indicate, as Mitchell, Flexner and Edsall thought, an index of certain alterations in the metabolism which lead up to a seizure, and this disturbance is situated in the muscles.

21. In addition to the references already given, the following will be found of interest:

Buzzard, E. Farquhar: Three Cases of Family Periodic Parlysis, Lancet, London, 1901, ii, 1564.

Atwood: C. E.: New York State Med. Jour., October, 1912.

The amount of undetermined nitrogen excreted in the urine is also increased. Our knowledge of this group of nitrogenous products is very meager. We do know that the so-called neutral sulphur and colloidal nitrogen are represented in this fraction. It would be of great interest to follow the amount of undetermined nitrogen excreted in the urine during an attack. It is possible that individuals affected with periodic paralysis may be unable to metabolize those products sufficiently and therefore an increased amount is excreted in the urine, or that they produce an excessive amount of these substances and that the attack is due to retention of these products.

COMMENT ON TABLE 2

In the seven-day metabolism period there was a loss of 0.17 gm. of sulphur. The urinary sulphur partition (total sulphate sulphur, inorganic sulphate sulphur, ethereal sulphate sulphur and neutral sul-

—AND PHOSPHORUS METABOLISM

Intake			Balance		
Phosphorus gm.	Calcium Oxid, gm.	Magnesium Oxid, gm.	Phosphorus gm.	Calcium Oxid, gm.	Magnesium Oxid, gm.
2.4	2.6	0.42	+ 0.08	+ 0.32	— 0.02
2.4	2.6	0.42	+ 0.06	+ 0.35	+ 0.02
2.4	2.6	0.42	— 0.03	+ 0.33	+ 0.04
2.4	2.6	0.47	— 0.08	+ 0.30	+ 0.11
2.2	2.1	0.42	— 0.37	— 0.16	+ 0.01
2.2	2.3	0.44	— 0.48	+0.05	+ 0.01
2.2	2.2	0.43	— 0.50	— 0.02	+ 0.02

phur) is normal in character. The fact that the neutral sulphur is not increased shows that this type of substance is not increased in the partition of the urine known as undetermined nitrogen. There were marked increased amounts of ethereal sulphates excreted on the third and fourth day coinciding with a period of constipation which we often find in patients placed on this diet.

COMMENTS ON TABLES 3 AND 4

In the seven days there was a loss of 1.32 gm. of phosphorus, a retention of 1.17 gm. of calcium oxid and 0.19 gm. of magnesium oxid. The fat metabolism is normal with an absorption of 92.8 per cent. of the ingested fat, and the percentage of neutral fat, fatty acids and soaps in the feces fat is normal.

SUMMARY

1. The clinical history and a metabolism study of seven days' duration on the Folin diet is described in a case of family periodic paralysis.

2. We have studied the nitrogen metabolism and urinary nitrogen partition (total nitrogen, urea nitrogen, ammonia nitrogen, uric acid nitrogen, creatinin nitrogen and undetermined nitrogen), the sulphur metabolism and urinary sulphur partition (total sulphates, inorganic sulphates, ethereal sulphates and neutral sulphur). We have also studied the calcium, magnesium, phosphorus and fat metabolism.

TABLE 4.—THE FAT METABOLISM

Period Days	Fat Intake gm.	Feces					Balance gm.
		Fat gm.	Percentage of Fat Absorbed	Percentage of Neutral Fat in Feces Fat	Percentage of Fatty Acid in Feces Fat	Percentage of Soaps in Feces Fat	
7	978	70	92.8	38	24	38	908

3. The only decided metabolic changes found was a marked decrease in the amount of creatinin and creatinin nitrogen excreted in the urine and a marked increase in the amount of undetermined nitrogen of the urine.

4. It would be of great value, using the same methods described in this paper, to repeat this study on a patient suffering from family periodic paralysis during an attack, so as to correlate the findings with those described in this paper.

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NOTE ON THE INCIDENCE OF STATUS LYMPHATICUS IN DEMENTIA PRAECOX*

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In a study of the clinical diagnosis of status lymphaticus based on the physical findings in 1,000 male patients in the alcoholic wards of Bellevue Hospital in New York, I noted[1] that among the patients referred to these wards were frequently to be found border-line cases, which on further study were properly classed as psychopathic cases instead of individuals of normal mentality who were toxic and irresponsible as a result of narcotic or alcoholic drug addictions.

Among these psychopathic patients, cases of dementia praecox were common, and in seeking an opportunity to study a larger group of such cases with a view to determining the incidence of status lymphaticus, I obtained permission through the courtesy of Dr. Wm. Mabon and the resident physicians at the State Asylum at Ward's Island to examine such inmates as were definitely classed as having dementia praecox.

No cases of doubtful diagnoses were considered, and in most instances the patients examined had been inmates for some years, and in no instance was a recent admission (within one month) classified and examined as dementia praecox.

In determining the diagnosis of status lymphaticus, I used the same criteria as I considered sufficient in the study above referred to, namely, in males, "a decided scantiness of hair on chin and upper lip, scanty axillary and sternal hair, scanty or feminine distribution of pubic hair, a slender thorax, rounded contour of upper arms and thighs, with an arching of the latter, hypoplastic external genitals, particularly if associated with cryptorchidism and a delicate velvety skin. The diagnosis is further confirmed if we find hyperplasia of the lymph tissue of nose, throat and tongue and an increase in the palpable cervical and axillary lymph-nodes."

I examined 208 men from 16 to 50 years of age, among whom sixty-one were found to exhibit the typical physical characteristics of status lymphaticus (29.3 per cent.); 147 were found to be physically normal (70.6 per cent.).

* Submitted for publication Nov. 24, 1914.

1. Emerson, Haven: The Archives Int. Med., 1914, xiii, 169.

Of the 61 status lymphaticus cases 9 were between 16 and 19 years of age; 27 were between 20 and 29; 15 were between 30 and 39; 8 were between 40 and 49; 2 were 50 years of age.

In the article already referred to, I ventured the unsupported statement that the incidence of status lymphaticus in cases of acute alienation in the first three decades was higher than among alcoholic and narcotic drug habitués, in whom I found an incidence of 22 per cent. This impression is now confirmed by the present report.

120 East Sixty-Second Street.

ARTIFICIAL PNEUMOTHORAX

WITH REPORT OF GAS ANALYSES AND EXPERIMENTS TO DETERMINE THE USE OF AIR OR NITROGEN *

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The present report will deal first with our experiences and results with artificial pneumothorax, and secondly with a series of gas analyses and animal experiments in regard to the use of air or nitrogen.

During the past two years the attempt has been made to produce an artificial pneumothorax in eighty-three patients with advanced pulmonary tuberculosis. In two cases the method of Brauer was attempted, in all others that of Forlanini.

The apparatus and method of procedure were practically similar to those so well described by Robinson and Floyd,[1] and by Hamman and Sloan;[2] therefore it will not be necessary to give the details here.

For the most part atmospheric air passed through sterile cotton filters has been the gas used. A series of cases, however, was treated with nitrogen for purposes of comparison, as will be shown in the latter half of this paper. Epinephrin (adrenalin, P. D. & Co.) and novocain were used in producing local anesthesia.

For convenience of analysis, the cases may be divided into the following groups:

I. Complete failure to find the pleural space (owing to extensive adhesions)		21 cases
II. Advanced cases, usually with cavity. Involvement of other lung not serious		25 cases
1. Remarkable benefit, loss fever, sputum, cough, etc.	18	
2. Some general benefit	6	
3. Very slight benefit	1	
4. No benefit whatever	0	
III. Far advanced; other lung involvement more serious		29 cases
1. Great benefit	7	
2. Fair degree of benefit	5	
3. Very slight benefit	8	
4. No benefit whatever	9	
IV. For hemorrhages		3 cases
1. Hemorrhages ceased but patient died later of other complications.		

* Submitted for publication June 19, 1914.

1. Robinson, Samuel, and Floyd, Cleaveland: Artificial Pneumothorax as a Treatment of Pulmonary Tuberculosis, THE ARCHIVES INT. MED., 1912, ix, 453.

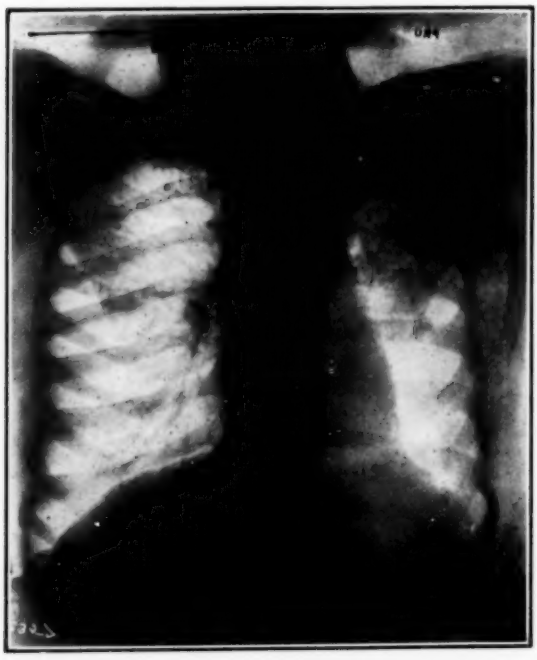
2. Hamman, L., and Sloan, M. F.: Induced Pneumothorax in the Treatment of Pulmonary Disease, Johns Hopkins Hosp. Bull., 1913, xxiv, 53.

2. Completely successful.
3. Hemorrhages ceased although very little collapse was obtained.

V. Lung abscesses (secondary to foreign body)..... 2 cases
1. Apparent complete cure.
2. Death due to bad general condition.

VI. Lung tumor (for diagnosis and relief of pain)..... 1 case

VII. Brauer method used after failure of Forlanini method..... 2 cases
1. No benefit.
2. Some slight benefit.
Collapse in each case only partial.



Retraction of the trachea to one side by apical fibrosis. For emphasis the trachea has been outlined by the radiologist, Dr. L. G. Brown. Fifteen years ago one of us had made a diagnosis of a dry cavity at the left apex. When two years ago the patient again came under observation the unusual position of the trachea was discovered.

The following incidents in this series of cases would seem of interest and importance:

1. In two cases which were considered for pneumothorax treatment, the Roentgen-ray examination revealed a mistake in the physical

diagnosis. In each case what had been considered an apical cavity was shown on the plates to be the trachea pulled to one side by apical fibrosis. (See illustration.)

2. Retraction of the trachea to one side may signify adhesions at the apex which will prevent collapse of that part of the lung should the remedy of pneumothorax be applied.

3. Within twenty-four hours of the first application of pneumothorax, spontaneous and complete pneumothorax followed in three patients, one in Class II and two in Class III. In no case, however, did this accident result fatally, although for a short time dangerous and alarming symptoms were present. We feel that this is a possible danger hitherto not sufficiently emphasized.

4. In the series the left lung much more frequently needed collapsing than the right.

5. Three brothers had their left lungs successfully collapsed.

6. In one patient with severe paroxysmal coughing the left lung was collapsed, with the exception of the cavity, which was located in the lower part of the upper lobe.

7. This patient later broke two ribs on the collapsed side as a result of his violent cough.

8. All cases should be handled at first like typhoid cases.

9. Over 900 injections of gas or air have been safely given.

10. No case of so-called pleural reflex has been encountered.

11. A slight case of air embolism probably occurred once. During a refilling, the patient turned slightly to observe the manometer. Unconsciousness and stertorous breathing occurred for a few moments. The next day a transient weakness of one hand was noticed.

12. An appreciable amount of fluid developed in ten cases, or 16 per cent. This was partly withdrawn in several cases on several occasions and usually lessened or disappeared. The fluid appeared late in the treatment.

13. The fluid became purulent, but culturally sterile, in three of these cases. Two of these were patients in whom the pneumothorax failed to give benefit and had been given up.

14. Two patients who refused the application of pneumothorax, and whose conditions seemed hopeless without attempting this remedy, and two in whom we were unable to induce it, are now in excellent condition, walking several miles a day, and with almost complete absence of expectoration.

15. Conclusions in regard to the amount of collapse of the affected lung can frequently be drawn by careful attention to the amount of sputum, the temperature, the pulse and the physical examination, with-

out the employment of the Roentgen ray. The Roentgen ray has been of scarcely any value in predicting the absence of adhesions or the possibility of collapse.

16. Experience has shown us that the compression should be kept up for probably several years. One patient after apparently complete recovery for two years began to have fever again as a result of too infrequent recompression. Hemorrhages recurred eight months later in a patient included in Group IV, who had only allowed the compression to be kept up three months.

CONCLUSIONS

The procedure of artificial pneumothorax is of undoubted value in many advanced cases of pulmonary tuberculosis. The dangers in its application with proper precautions would seem negligible, except as stated in Paragraph 3 above. The necessity for keeping up the compression over a long period of time is a serious drawback, as is also the possible annoyance to the patient of the development of fluid. For the present every known method should be very thoroughly tried out before suggesting pneumothorax to our patients.

In May, 1912, J. S. Haldane, the Oxford physiologist, expressed the opinion to one of us that the use of nitrogen, as advocated for artificial pneumothorax, could have little, if any, advantage over the use of air, because in either case diffusion of gases would so rapidly occur.

Little can be found in the literature regarding the analyses of the gaseous contents of the chest in cases of artificial pneumothorax and the employment of nitrogen instead of atmospheric air would seem to be based on theoretical rather than experimental grounds.

Wells[3] states that when air enters a closed pleural cavity, and no effusion follows, it is slowly absorbed. At first there is a rapid absorption of oxygen which is partly replaced by carbon dioxid with a resulting relative increase in nitrogen. Ordinarily, the entrance of air into the pleural cavity is followed by an effusion either serous or purulent which may modify the composition of the gases. Purulent pneumothorax generally shows more carbon dioxid than the serous form.

Hamman[2] states that the normal pleural cavity absorbs from 80 to 100 c.c. nitrogen per day; after the pneumothorax has existed for some months it absorbs from 25 to 50 c.c.

Tobiesen[4] has published a few gas analyses, and in a very interesting paper has given a short historical sketch which we briefly abstract.

3. Wells: Chemical Pathology.

4. Tobiesen, T.: Untersuchungen über Pneumothorax luft, Beitr. z. Klin. d. Tuberk., 1911, xix, 451; ibid., 1911, xxi, 109.

In 1805 Itart described the pathological condition of pneumothorax and gave it the present name.

In 1823 Davy for the first time analyzed pneumothorax air from a patient. He also injected air into the pleural cavity of animals and then withdrew samples and analyzed them. He found that oxygen became absorbed and that carbon dioxid diffused out into the pleural space.

Demarquay and Leconte were able to decide by gas examinations whether spontaneous pneumothorax cases were "open" or "closed." They state that nitrogen is slowly absorbed by the pleural wall.

Tobiesen reports sixteen gas analyses in seven cases of spontaneous pneumothorax, five analyses in three cases of artificial pneumothorax induced by atmospheric air, and six analyses in three cases induced by nitrogen gas.

The nitrogen gas employed yielded the following analysis: oxygen 4.31 per cent., carbon dioxid 0.62 per cent. and nitrogen 95.07 per cent.

Table 1 depicts Tobiesen's results.

TABLE 1.—RESULTS OF TOBIESEN'S GAS ANALYSIS IN CASES OF PNEUMOTHORAX, NATURAL AND ARTIFICIAL

Case No.	Total Air Injected	Days Since Injected	Amount at Last Injection	O_2	Per Cent. CO_2	N
8	1. 2,850	8	1,000	2.48	6.32	91.20
	2. 4,650	7	800	2.86	....	90.62
9	1. 2,450	6	800	0.95	7.04	92.01
10	1. 2,600	6	500	0.71	8.32	90.97
	2. 4,300	14	600	0.69	9.31	90.00
	Total Nitrogen Injected					
11	1. 4,200	7	300	0.09	10.26	89.65
	2. 4,500	9	300	0.05	10.12	89.83
12	1. ?	14	700	2.67	7.15	90.18
	2.	14	500	2.82	6.98	90.20
13	1. 1,260	3	320	1.96	7.14	90.90
	2. 2,060	5	400	1.66	7.39	90.95

On analyzing these figures little difference can be detected in favor of nitrogen; in fact, the amount of nitrogen determined in the cases in which air had been employed reads the higher.

It seemed to us worth while, therefore, especially in consideration of Haldane's unusual knowledge regarding the lungs and gaseous diffusion, to carry out a series of analyses with patients undergoing treatment by the application of artificial pneumothorax.

From the first it was realized that it would be impossible to regain and measure the whole amount of gas injected in patients and the final proof, therefore, of any advantage of nitrogen gas over atmospheric air might be lacking. We foresaw that simple analyses of the samples

withdrawn from the pleural space could yield only indirect and incomplete evidence.

The first gas analyses were made with samples obtained from a large dog in which artificial pneuthorax had been induced with nitrogen withdrawn from a cylinder obtained from a commercial house.

The results[5] of the analysis of this so-called pure nitrogen obtained directly from the cylinder were startling: oxygen 13.98 per cent., carbon dioxid none and nitrogen 86.02 per cent.

TABLE 2.—Experiment on Large Dog

Date	Gas Removed c.c.	Yielding Per Cent.			Gas Injected c.c.
		O_2	CO_2	N	
3/23/13	.....	.....	.....	.....	400
3/24/13	30	14.5	Trace	85.5	500
3/25/13	35	15.06	3.74	81.2	700
3/28/13	35	10.42	5.70	83.88	

This experiment clearly showed that carbon dioxid was gradually diffused out into pleural space.

We now decided to manufacture our own nitrogen, and the following method was employed, a method which is convenient, cheap and productive of gas in a very pure form: two parts of a 40 per cent. solution of sodium nitrite are mixed with three parts each of a 20 per cent. solution of ammonium sulphate and a 20 per cent. solution of potassium dichromate. This is heated gently and passed through a potassium pyrogallate solution and through sulphuric acid and collected by displacement of water. As will be seen by the tables, we were enabled to procure, by this means, nitrogen about 99 per cent. pure.

In a few cases we used oxygen for the production of pneumothorax. The method used for preparing oxygen was to mix four parts potassium chlorate with one part manganese oxid. This is heated slowly in a test-tube and collected by displacement of water.

A series of patients treated with nitrogen were now compared with a series of patients treated with air. The method of procedure was as follows:

The samples of the gas mixtures were always withdrawn from the thorax before introducing a fresh supply. The needle having been inserted as usual and the oscillations obtained, the tube to the bottle containing the air, or gas, to be injected was clamped off close to the

5. Haldane and his co-workers had a similar experience with commercial oxygen during their expedition to Pike's Peak in 1911.

needle, and the gas-sampling tube attached to the other projection of the needle, which could be opened by a stop-cock. The sampling tube had a capacity of about 30 c.c. and was provided at each end with a two-way stop-cock. The tube was previously completely filled with mercury and the gas drawn from the pleural cavity into the gas receiver by allowing the mercury to escape through the lower end of the tube.

The sample thus obtained was analyzed with the smaller Haldane gas analysis apparatus.[6] This is essentially as follows: The sample is drawn by mercury suction into a graduated buret and the amount of gas read. By means of mercury the gas is now forced over a connecting tube into a bulb of 15 per cent. caustic potash which absorbs the carbon dioxid. The difference is now read on the graduated buret and the percentage of carbon dioxid thus obtained. The gas is then run over into a bulb containing a 10 per cent. solution of potassium pyrogallate, which absorbs the oxygen.

The difference between the amount left after absorption of carbon dioxid and the amount now left is the quantity of oxygen in the sample.

For all practical purposes the remaining gas may be considered nitrogen.

Tables 3 to 8 typify individual cases treated with nitrogen gas and with atmospheric air. These tables would indicate that within from twenty-four to forty-eight hours, in the nitrogen-treated cases, about 4 per cent. oxygen and about 8 per cent. carbon dioxid appear in the pleural space, or, in other words, the nitrogen becomes diluted at least 10 per cent. If the law of diffusion of gases holds good in these cases, then some of the pure nitrogen must diffuse in the opposite direction into the gases of the lungs tending to establish equilibrium.

When atmospheric air is injected, within a similar period of time practically exactly similar analyses are obtained as in the nitrogen cases. Therefore, diffusion of oxygen to at least 15 per cent. has taken place into the blood. On the other hand, diffusion of carbon dioxid to about 7 per cent. from the blood and of nitrogen to about 10 per cent. from the lung alveolar air has occurred into the pleural space. The treated lung being collapsed and compressed, equilibrium is probably established through the mediastinal pleura from the alveolar air of the opposite lung. In fact, the percentages in the two types of cases run parallel and no essential difference can be noted. Those who analyzed the gas sample could not at any stage tell whether the patient had been treated with pure nitrogen or with pure air.

6. Described in Haldane's "Methods of Air Analysis." London, Charles Griffin & Co., ltd., 1912.

TABLE 3.—Case 51, Treated with Nitrogen Gas

Date	Injection No.	Amount Given	Analysis of Gas Removed			Analysis of Gas Given			Pressure in Cm. Water	
			O_2	CO_2	N	O_2	CO_2	N	Before	After
9/20/13	1	400	....	....	.....	4.25	1.64	94.11	−2	−2
9/22/13	2	600	8.66	6.55	84.79	0.15	0.52	99.33	−2	−1
9/24/13	3	700	4.08	6.74	88.58	0.15	0.92	98.92	0	+1
9/29/13	4	800	3.08	7.26	89.66	0.1	0.61	99.29	0	+2
10/ 6/13	5	300	1.91	8.11	89.98	0.31	0.13	98.56	0	+2
10/15/13	6	400	1.31	9.02	89.67	2.75	0.41	96.84	0	+3
10/31/13	7	800	1.52	8.01	90.47	....	....	.....	0	+4

TABLE 4.—Case 47, Treated with Atmospheric Air

Date	Injection No.	Amount Given	Analysis of Gas Removed			Analysis of Gas Given			Pressure in Cm. Water	
			O_2	CO_2	N	O_2	CO_2	N	Before	After
7/16/13	1	200	....	....	.....	20.93	0.03	79.04	−2	−2
7/17/13	2	300	7.92	6.85	85.23	....	....	.....	−3	0
7/18/13	3	500	6.64	7.82	85.54	....	....	.....	−2	0
7/21/13	4	800	4.17	7.08	88.75	....	....	.....	−2	+1
7/26/13	5	800	2.15	7.83	90.02	....	....	.....	−1	+1
8/ 2/13	6	1,000	2.31	7.47	90.22	....	....	.....	−0	+2
8/11/13	7	1,100	1.97	8.00	90.03	....	....	.....	−1	+3
8/21/13	8	1,250	2.28	8.20	89.52	....	....	.....	−1	+4
9/ 2/13	9	1,250	1.86	8.33	89.81	....	....	.....	0	+5
9/16/13	10	1,400	1.58	8.28	90.14	....	....	.....	−1	+4
10/ 6/13	11	1,200	2.35	8.70	88.95	....	....	.....	0	+5

TABLE 5.—Case 52, Treated with Nitrogen Gas

Date	Injection No.	Amount Given	Analysis of Gas Removed			Analysis of Gas Given			Pressure in Cm. Water	
			O_2	CO_2	N	O_2	CO_2	N	Before	After
10/14/13	1	500	....	....	.....	0.61	0.72	98.67	− 2	0
10/18/13	2	600	4.84	7.33	87.83	0.10	0.82	99.08	− 2	−2
10/22/13	3	700	4.81	6.57	88.62	....	....	.....	− 1	+4
10/28/13	4	600	....	....	.....	....	....	.....	0	+4
11/ 2/13	5	700	3.67	5.96	90.37	....	....	.....	− 1	+4
11/ 7/13	6	1,200	3.75	7.11	89.14	....	....	.....	−½	+7
11/12/13	7	600	....	....	.....	....	....	.....	+ 1	+7
11/17/13	8	500	3.70	6.41	89.89	....	....	.....	+ 4	+9
11/24/13	9	600	4.39	6.65	88.96	....	....	.....	+ 3	+7
12/ 6/13	10	800	3.97	6.16	89.87	....	....	.....	+ 2	+7

TABLE 6.—Case 44, Treated with Atmospheric Air

Date	Injection No.	Amount Given	Analysis of Gas Removed			Analysis of Gas Given			Pressure in Cm. Water	
			O_2	CO_2	N	O_2	CO_2	N	Before	After
6/30/13	1	350	....	....	.....	20.93	0.03	79.04	—3	—3
7/ 2/13	2	200	5.63	6.18	88.19	....	....	.....	0	+1
7/ 5/13	3	400	4.66	6.07	89.27	....	....	.....	—1	+2
7/ 9/13	4	400	3.07	7.23	89.70	....	....	.....	0	+3
7/15/13	5	600	2.09	7.63	90.28	....	....	.....	—1	+3
7/22/13	6	650	2.12	8.16	89.72	....	....	.....	—1	+4
7/30/13	7	600	2.79	7.84	89.87	....	....	.....	—1	+3
8/ 8/13	8	700	2.86	8.29	88.85	....	....	.....	—1	+4
8/18/13	9	600	1.45	8.83	89.72	....	....	.....	—2	+3
8/28/13	10	650	1.80	8.84	89.36	....	....	.....	—1	+4
9/11/13	11	650	1.67	8.79	89.54	....	....	.....	—1	+4

TABLE 7.—Case 46, Treated with Atmospheric Air

Date	Injection No.	Amount Given	Analysis of Gas Removed			Analysis of Gas Given			Pressure in Cm. Water	
			O_2	CO_2	N	O_2	CO_2	N	Before	After
7/15/13	1	150	....	....	.....	20.93	0.03	79.04	—2	—2
7/17/13	2	200	5.07	8.44	86.49	....	....	.....	—2	0
7/19/13	3	300	....	....	.....	....	....	.....	—2	0
7/22/13	4	450	3.85	6.63	89.52	....	....	.....	—1	—1
7/26/13	5	500	....	....	.....	....	....	.....	—1	—3
8/ 2/13	6	600	2.55	7.60	89.85	....	....	.....	—1	—5
8/11/13	7	900	2.22	7.51	90.27	....	....	.....	—1	—6
8/21/13	8	800	2.60	2.85	90.55	....	....	.....	—1	—5

TABLE 8.—Case 54, Treated with Atmospheric Air

Date	Injection No.	Amount Given	Analysis of Gas Removed			Analysis of Gas Given			Pressure in Cm. Water	
			O_2	CO_2	N	O_2	CO_2	N	Before	After
10/15/13	1	300	....	....	.....	2.75	0.61	96.64	—6	—2
10/17/13	2	500	2.44	7.15	90.41	....	....	.....	—4	—2
10/21/13	3	800	....	....	.....	....	....	.....	—2	—2
	4	800	1.46	9.56	88.98	....	....	.....	—2	—2
	5	750	0.80	10.03	89.17	....	....	.....	—3	—3
	6	900	0.70	10.53	88.77	....	....	.....	0	—5
	7	1,000	0.71	9.85	89.44	....	....	.....	—2	—6
	8	800	1.11	9.61	89.28	....	....	.....	—2	—6

TABLE 9.—Nitrogen Cases

No. of Case	Date	No. Injection	Amount Given to Date in c.c.	Days Since Last Injection	Amt. Given in c.c.	Gas Analysis			Pressure	
						CO_2	O_2	N	Before	After
50	8/16/13	..	.....	15	800	8.36	3.96	87.68	—2	— 5
50	8/27/13	..	.....	11	1,000	7.53	3.05	89.42	—3	— 9
50	9/12/13	..	.....	16	950	7.97	4.73	87.50	—2	— 8
51	9/22/13	2	400	2	600	6.55	8.66	84.79	—2	0
51	9/24/13	3	1,000	2	700	6.74	4.68	88.58	0	— 1
50	9/27/13	..	.....	15	900	7.98	4.61	87.41	0	— 8
50	10/ 3/13	..	.....	6	800	7.74	5.06	87.20	—1	— 9
51	9/29/13	4	1,700	5	800	7.26	3.08	.76	0	— 2
51	10/ 6/13	5	2,500	8	300	8.11	1.91	.....	0	— 2
51	10/15/13	6	2,800	9	400	9.02	1.31	.....	0	— 3
54	10/17/13	2	300	2	500	7.10	2.44	.....	—4	— 2
52	10/18/13	3	800	4	600	7.33	4.84	87.83	—2	— 2
52	10/22/13	4	1,400	4	700	6.57	4.81	.....	—1	— 4
54	10/28/13	4	.....	7	800	9.56	1.46	88.98	—2	— 2
53	10/29/13	3	1,000	7	800	6.54	4.98	.....	—2	— 3
51	10/31/13	7	3,200	16	800	8.01	1.52	90.47	0	— 4
52	11/ 2/13	6	2,700	5	700	5.92	3.67	90.37	—1	— 5
54	11/ 3/13	5	2,400	6	750	10.03	0.80	89.17	—1	— 3
52	11/ 7/13	7	3,400	5	1,200	7.11	3.75	89.14	—1	— 7
53	11/ 7/13	4	1,800	9	900	6.66	4.50	88.84	—2	— 5
50	11/ 7/13	..	.....	19	900	7.80	5.05	87.15	0	— 8
54	11/ 8/13	6	3,150	5	900	10.53	0.70	88.77	0	— 5
54	11/13/13	7	4.050	5	1,000	9.85	0.71	89.44	—2	— 6
52	11/17/13	9	5,200	5	500	6.41	3.70	89.89	—4	— 9
53	11/17/13	5	2,700	10	1,000	4.51	7.09	89.40	—3	—10
54	11/22/13	8	5,050	9	800	9.61	1.11	89.28	—2	— 6
52	11/24/13	10	5,700	7	600	6.65	4.39	88.96	—3	— 7
53	11/29/13	6	3,700	12	650	6.86	5.22	87.92	0	— 7
50	11/29/13	..	.....	22	650	8.05	4.82	87.13	—1	— 8
52	12/ 6/13	11	6,300	12	800	6.16	3.97	89.87	—2	— 7
(a)	6/29/13	9	4,215	6	350	10.87	1.10	88.03		
(b)	7/ 9/13	19	10,445	35	125	12.40	0.419	87.19		
(c)	7/ 9/13	5	1,500	4	580	6.81	2.37	90.82		
(a)	7/28/13	12	5,315	12	300	10.59	1.02	88.39		
(c)	7/28/13	19	3,280	5	...	7.28	2.34	90.38		
(d)	8/20/13	4	1,000	6	250	7.43	5.51	87.06		
(a)	8/20/13	15	6,715	10	400	11.08	*	88.92		
(b)	10/ 8/13	21	10,660	60	...	11.21	2.58	86.21		
(a)	10/ 8/13	19	7,965	18	500	10.06	1.73	88.21		

* Trace.

TABLE 10.—Atmospheric Air Cases

No. of Case	Date	No. Injection	Amount Given to Date in c.c.	Days Since Last Injection	Amt. Given in c.c.	Gas Analysis			Pressure	
						CO_2	O_2	N	Before	After
26	6/21/13	13	112,000	21	850	6.80	4.51	88.69	—1	— 5
37	6/23/13	5	2,050	15	900	6.35	4.34	89.31	—1	— 2
34	6/23/13	7	4,850	15	800	6.42	4.23	89.35	0	— 4
42	6/24/13	5	1,800	7	600	6.61	3.46	89.93	—1	— 2
40	6/25/13	7	3,700	12	900	8.71	1.40	89.89	0	— 5
13	6/26/13	14	113,000	10	1,000	5.31	7.66	87.03	—8	— 8
41	6/26/13	5	2,100	23	700	7.47	4.25	88.28	—1	— 4
36	6/27/13	7	3,550	11	600	8.65	1.69	89.66	—1	— 3
19	6/28/13	15	.....	25	350	9.56	1.39	89.05	—1	—10
27	6/30/13	14	7,000	23	300	6.87	2.09	91.04	—1	—12
14	6/30/13	19	10,500	28	300	6.95	4.51	88.54	—2	—15
21	6/30/13	12	11,800	20	1,100	6.73	3.73	89.54	—2	— 5
44	7/ 2/13	2	350	2	200	6.18	5.63	88.19	0	— 1
33	7/ 2/13	9	7,800	14	900	8.16	4.33	87.51	—1	— 5
25	7/ 3/13	11	.....	37	600	10.13	0.67	89.20	—2	— 6
2	7/ 3/13	..	.....	33	800	6.67	3.02	90.31	—2	—10
36	7/ 5/13	8	4,100	8	650	9.34	1.49	89.17	—2	— 8
44	7/ 5/13	3	550	3	.....	6.07	4.66	89.27	—1	— 2
40	7/ 8/13	8	5,200	13	700	9.31	1.64	89.05	0	— 5
7	7/ 8/13	15	11,800	40	650	12.59	0.89	86.52	—1	—10
22	7/ 9/13	11	7,700	39	700	13.59	1.12	85.29	—1	— 6
44	7/ 9/13	4	950	4	400	7.23	3.07	89.70	0	— 3
41	7/11/13	6	2,800	15	700	5.96	6.41	87.63	0	— 7
34	7/11/13	8	5,600	18	950	6.52	5.47	88.01	—2	— 3
43	7/12/13	..	.....	23	250	12.50	0.75	86.75	—1	— 7
36	7/13/13	9	4,800	8	650	9.01	1.52	89.47	0	— 4
44	7/15/13	5	1,350	6	600	7.63	2.09	90.28	—1	— 3
26	7/14/13	14	11,900	23	1,050	7.81	3.56	88.63	—2	— 4
46	7/17/13	2	150	2	.....	5.07	8.44	86.49	—2	0
47	7/17/13	2	200	1	300	6.85	7.92	85.23	—3	0
36	7/18/13	10	5,450	5	725	6.25	3.56	90.69	—1	— 8
33	7/18/13	10	8,700	16	1,000	10.49	3.83	85.68	—1	— 7
31	7/18/13	9	6,600	28	1,000	10.57	0.56	88.87	—1	— 7
47	7/18/13	3	500	1	500	7.82	6.64	85.54	—2	0
46	7/22/13	4	650	3	450	6.63	3.85	89.52	—1	— 1
44	7/22/13	6	1,950	7	650	8.16	2.12	89.72	—1	— 4
47	7/21/12	4	1,000	3	800	7.08	4.17	88.75	—2	— 1
40	7/24/13	9	5,900	16	800	9.53	1.36	89.11	0	— 5
27	7/24/13	15	7,300	24	250	7.37	1.92	90.71	0	—14
48	7/25/13	3	600	4	600	5.67	6.70	87.63	—1	— 3
47	7/26/13	5	1,800	5	800	7.83	2.15	90.02	—1	— 1
25	7/27/13	..	.....	24	700	10.39	1.37	88.24	—1	— 6
44	7/30/13	7	2,600	8	600	7.84	2.29	89.87	—1	— 3
21	7/30/13	13	12,900	31	1,100	6.46	4.55	88.99	—2	— 5
42	8/ 1/13	8	3,600	16	900	7.17	2.43	90.40	—1	— 6
46	8/ 2/13	6	1,400	7	600	7.60	2.55	89.85	—1	— 5
40	8/ 2/13	11	6,700	9	950	8.98	4.03	86.99	—1	— 5
14	8/ 2/13	20	10,800	33	500	7.61	4.62	87.77	0	—18
47	8/ 2/13	6	2,600	7	1,000	7.47	2.31	90.22	0	— 2
5	8/ 2/13	11	4,600	84	300	13.04	2.79	84.17	—6	—14
7	8/ 4/13	16	12,450	27	700	10.08	5.64	84.28	—1	—10
48	8/ 7/13	5	.....	8	800	6.77	5.76	87.47	0	— 6
44	8/ 8/13	8	3,200	9	700	8.29	2.86	88.85	—1	— 4
26	8/ 9/13	15	12,950	26	1,000	8.57	2.79	88.64	—2	— 5

TABLE 10.—(Continued)

No. of Case	Date	No. Injection	Amount Given to Date in c.c.	Days Since Last Injection	Amt. Given in c.c.	Gas Analysis			Pressure	
						CO_2	O_2	N	Before	After
24	8/ 9/13	13	14,800	25	700	6.89	3.66	89.45	—3	— 5
46	8/11/13	7	2,000	9	900	7.51	2.22	90.27	—1	— 6
47	8/11/13	7	3,600	9	1,100	8.00	1.97	90.03	—1	— 3
12	8/14/13	14	11,500	75	950	6.26	5.74	88.00	—5	— 3
2	8/15/13	..	.....	43	800	7.55	3.94	88.51	—2	—12
43	8/16/13	..	.....	36	550	12.50	0.72	86.45	—2	—16
33	8/16/13	11	9,650	29	800	9.30	3.35	87.35	—2	— 7
25	.....	..	.....	20	600	10.88	*	89.12	—2	— 7
44	8/18/13	9	3,900	10	600	8.83	1.45	89.72	—2	— 3
47	8/21/13	8	4,700	10	1,250	8.20	2.28	89.52	—1	— 4
46	8/21/13	8	3,100	10	800	6.85	2.60	90.55	—1	— 5
40	8/21/13	11	7,050	19	900	8.44	2.24	89.32	—1	— 4
14	8/26/13	21	.....	23	450	8.25	3.80	87.95	0	—18
48	.....	7	3,700	10	900	6.90	5.28	87.82	—1	— 8
44	8/28/13	10	4,500	10	650	8.84	1.80	89.36	—1	— 4
28	.....	11	10,050	35	1,250	11.11	0.70	88.19	—2	— 6
47	9/ 2/13	9	5,950	11	1,250	8.33	1.86	89.81	0	— 5
48	9/ 6/13	8	4,600	12	800	5.72	8.71	85.52	—2	— 5
26	9/ 7/13	16	15,100	29	1,000	8.66	2.28	89.06	—2	— 4
21	.....	14	12,900	39	1,000	7.64	3.24	89.12	—4	— 5
33	9/12/13	12	10,450	27	800	9.31	3.60	87.09	—4	— 3
44	.....	11	5,150	15	650	8.79	1.67	89.54	—1	— 4
13	9/18/13	..	.....	34	700	7.28	4.82	87.90	—2	— 6
48	9/19/13	9	5,400	13	650	5.72	6.24	88.04	0	— 5
2	.....	..	.....	35	700	9.37	2.06	88.57	—2	— 4
26	9/20/13	17	16,100	13	650	8.96	1.73	89.31	—1	— 5
40	9/23/13	12	7,950	18	1,000	8.59	1.41	90.00	—1	— 4
7	.....	..	.....	50	1,400	9.07	3.71	87.22	—5	— 5
47	10/ 6/13	11	8,600	20	1,200	8.70	2.35	88.95	—0	— 5
56	11/23/12	3	900	3	900	7.43	3.10	89.47	2	— 1
48	12/ 2/13	10	5,950	15	600	7.14	3.87	88.99	0	— 4

* Trace.

TABLE 11.—Oxygen Cases

No. of Case	Date	No. Injection	Amount Given to Date in c.c.	Days Since Last Injection	Amt. Given in c.c.	Gas Analysis			Pressure	
						CO_2	O_2	N	Before	After
58	12/ 3/13	2	500	2	900	4.16	24.04	71.80		
58	12/ 8/13	3	1,400	5	1,200	4.53	19.77	75.70	—3	— 1
58	12/11/13	4	2,600	3	1,000	2.64	21.76	75.40	—3	0
59	12/ 6/12	2	300	3	500	1.02	15.25	83.73		
59	12/11/13	3	800	5	500	6.52	7.41	86.07	—5	— 2

Analysis of gas given 96.56 pure.

Clinically, the amount of gas necessary to produce and maintain a pneumothorax varied greatly in individual cases and seemed more dependent on the size of the chest, the extent of the adhesions, and the rate of diffusion through the tissues of the individual than on the nature of the gas given. On the whole, it may have seemed necessary to use a trifle less nitrogen than air to maintain a definite positive pressure in the pleural cavity. Still in one patient in whom pneumothorax was induced and kept up with nitrogen, we had to make more frequent injections to keep down her temperature and expectoration than in another patient in the same house treated with air and with similar lung involvement. Thus the rapidity of absorption in each case seems to be a law unto itself.

The oxygen cases are especially noteworthy from the discovery of the large addition of nitrogen which must have diffused into the pleural space. Since blood contains only a small percentage of nitrogen (about 2.4 per cent.), diffusion must take place between alveolar air and pleural space to establish equilibrium. It would, therefore, seem certain that whatever gas is used for the production of pneumothorax, it does not long remain pure; for Nature rapidly changes it until an analysis yields the equivalent of alveolar air. At our elevation (6,000 feet) alveolar air averages carbon dioxid 6 per cent., oxygen 14 per cent. and nitrogen 80 per cent.

In general, the longer the time between injections, the higher the percentage of carbon dioxid and the lower the percentage of oxygen, the former tending to reach 10 per cent. and the latter from 1 per cent. to zero.

For a series of crucial experiments, we performed the operation of pneumothorax on monkeys which had been used for experimental tuberculous infection.

The first result obtained follows:

EXPERIMENT 1.—The right lungs of two monkeys (*Macacus rhesus*) of equal size and weight were collapsed under ether, one with air and the other with nitrogen as the figures indicate.

	MONKEY 1		MONKEY 2	
Day	Air, c.c.	Pressure	Nitrogen, c.c.	Pressure
1st	45	—	45	—
2d	80	+	80	+

Analysis of nitrogen direct from generator: carbon dioxid 0.22, oxygen 0.32, nitrogen 99.46.

Analysis of nitrogen direct from apparatus used for injection: carbon dioxid 0.83, oxygen 4.89, nitrogen 94.28.

On the fourth day both monkeys were killed. The right pleural spaces were immediately filled cautiously with water through a fine needle and simultaneously the gaseous contents which escaped through another needle, were carefully collected by displacement of water.

The amount collected from No. 1 measured 83 c.c. and on analysis gave carbon dioxid 8.06, oxygen 4.24 and nitrogen 87.70; that from No. 2 measured 92 c.c. and on analysis gave carbon dioxid 8.52, oxygen 5.61 and nitrogen 85.87.

It is thus seen that forty-eight hours after positive pressure had been induced, the balance in favor of the use of nitrogen was only 7 per cent. The analysis of the gases removed is practically the same in each instance.

EXPERIMENT 2.—The same procedure was followed as in Experiment 1, but the injections were continued for a longer time so that conditions more nearly approximating the usual pneumothorax treatment would be reached.

	Monkey 7, Weight 2,700 gm.		Monkey 10, Weight 3,400 gm.	
Day	Nitrogen, c.c.	Pressure	Air, c.c.	Pressure
1st	45	—	45	—
3d	80*	—	80	—
6th	65	+(1 cm.)	65	—(1 cm.)
9th†	50	+(2 cm.)	50	—(1 cm.)
12th	70	+(2 cm.)	110	+(2 cm.)

* Analysis of nitrogen given from injection apparatus 97 per cent. pure.

† As Monkey 10 was somewhat the larger, it was decided to inject enough air next time (twelfth day) to bring the positive pressure the same in each animal.

Total nitrogen injected, No. 7, 310 c.c.
Total air injected, No. 10, 350 c.c.

Fifteenth day animals killed by chloroform. Gas contents of right pleural spaces collected as before.

	N (%)	O_2 (%)	CO_2 (%)
Monkey 7, 140 c.c. recovered, analyzing	86.74	3.57	9.69
Monkey 10, 181 c.c. recovered, analyzing	85.09	4.85	10.06

Again the gas analyses of the contents removed are practically the same in each instance. These samples were collected direct from the pleural spaces by the mercury pump method above described.

Monkey 7, of the total nitrogen injected, 46 per cent. was recovered.
Monkey 10, of the total air injected, 51 per cent. was recovered.

In all these monkeys post-mortem examination was made to determine that the technic had been accuraate.

CONCLUSIONS

We feel that the conjecture of Haldane is fully upheld by the foregoing determinations and experiments, and that little if any advantage is to be gained by the employment of nitrogen rather than atmospheric air for the production of artificial pneumothorax.

We desire to acknowledge, among the foregoing, cases kindly referred to us by Drs. Boyd, Forster, Hoagland, Martin, Timmons, Stough, Shivers and Swan. Our thanks are due to Mr. and Mrs. B. C. Allen and Mr. Richard F. Howe of Colorado Springs for generous financial support. To Dr. E. C. Schneider and to the laboratories of Colorado College we are under obligations for the facilities allowed us for the gas determinations.

Cragmor Sanatorium.

THE EFFECT OF STRYCHNIN, CAFFEIN, ATROPIN AND CAMPHOR ON THE RESPIRATION AND RESPIRATORY METABOLISM IN NORMAL HUMAN SUBJECTS *

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The effects which drugs may, conceivably, have on respiration are of four varieties.

1. They may either stimulate or depress the respiratory center.

2. They may alter respiration indirectly by increasing or decreasing metabolism.

3. They may alter the general character of breathing, rapid and shallow or slow and deep, or thoracic or abdominal by producing changes in the mechanical conditions within the chest or abdomen, by acting on the circulation, the abdominal viscera or the thoracic or abdominal musculatures.

4. They also may alter respiration by acting as bronchoconstrictors or dilators, and hence altering the dead space in the chest, which necessitates a compensatory change in the ventilation.

The data which must be obtained in studying these various actions are: the carbon dioxid elimination and the oxygen absorption, which give the metabolism; the carbon dioxid tension of the alveolar air and the ventilation of the lungs, which give information as to the excitability of the respiratory center, and the relation of ventilation to respiration rate, which gives the character of the breathing. In regard to ventilation we wish to emphasize the point, discussed in a previous communication by one of us (D. L. E.[1]), that it is the alveolar and not the total ventilation, which is of importance. The chief function of the respiratory center is to maintain a ventilation of the lung alveolae sufficient to keep the tension of carbon dioxid at a definite level. What this level shall be depends on the excitability of the center. The amount of ventilation necessary to accomplish this result depends on the elimination of carbon dioxid, and hence on the metabolism. Haldane[2] and

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1. Edsall, D. L.: The Clinical Study of Respiration, Med. Communications, Mass. Med. Soc., 1912, xxiii, 19.
2. Haldane, J. S., and Priestley, J. G.: The Regulation of Lung Ventilation, Jour. Physiol., 1905, xxxii, 224.

his co-workers have definitely shown that it is the tension of carbon dioxid in the arterial blood, and hence in the alveolar air (for the tension of gases in the blood leaving the lungs is always practically in equilibrium with that of the alveolar air), which regulates lung ventilation, and that the tension itself will depend on the excitability of the center. In other words, the ventilation of the lungs will always be such that the carbon dioxid tension of the alveolar air is kept at whatever level the center requires. This truth having been established, the following relationships will become apparent: First, the elimination of carbon dioxid remaining constant, changes in the alveolar ventilation will indicate changes in the excitability of the center. Secondly, the excitability of the center remaining the same, changes in the alveolar ventilation will indicate changes in the carbon dioxid elimination. Also, provided that no acidosis is present — and this assumption is reasonable in the case of normal subjects — or if present, that it remains constant during the period of observation, changes in the carbon dioxid tension of the alveolar air may always be interpreted as indicating a change in the excitability of the respiratory center.

From the foregoing remarks it will become clear, we hope, that it is the alveolar ventilation and the carbon dioxid tension, rather than the total ventilation and respiration rate, which are of chief importance, in studying the condition of the respiratory center. We wish to emphasize this point particularly, because in most previous work it has been the total ventilation and rate that have been chiefly studied.

The object of the present research has been, therefore, to investigate the action of the drugs commonly used as respiratory stimulants, bearing in mind the points brought out above, namely, that the alveolar ventilation and the carbon dioxid tension of the alveolar air are the factors which give information regarding the center, and that the total ventilation and rate may be subject to wide variation without there being any change in the excitability of the center, and therefore, that wrong deductions are likely to be drawn when the total ventilation and rate are alone studied. We do not wish to underestimate the importance of observing respiration rate, but we do wish to call attention to the fact that rate has nothing to do, per se, with lung ventilation. Ventilation of the alveolae is carried out entirely, except in such cases of abnormal hyperpnea as that due to pain or emotion, through the chemical stimulation of the respiratory center by the hormone carbon dioxid. Also it might be well to add here, that it has been recently shown by Hasselbalch[3] and others that this action is due merely to the

3. Hasselbalch, K. A.: Neutralitätsregulation und Reizbarkeit des Atemzentrums in ihren Wirkung auf die Köhlensaurespannung des Blutes, Biochem. Ztschr., 1912, xlvi, 403.

fact that carbon dioxid (in solution) is an acid; any other acid will also stimulate the center. In other words, it is apparently the hydrogen ion concentration of the blood reaching the center that stimulates it. When there is an increase in the production of carbon dioxid, as during muscular work, the carbon dioxid content of the blood reaching the center will increase, and hence the acidity will increase until the center by increasing ventilation has restored the alveolar carbon dioxid tension to its former level. This increase in ventilation may be accomplished by an increase in rate, or depth, or both. What determines the method by which ventilation shall be increased, in other words, whether it shall be rate, depth, or both that are increased, is, in all probability, regulated through nervous channels. For instance, the demand for an increased ventilation having been received by the center chemically, the carrying out of this function is probably controlled by afferent nervous impulses. The character of the breathing must accommodate itself to the mechanical condition in the chest and abdomen. Thus in abdominal distention deep breathing may be impossible, and hence a demand for increased ventilation will have to be met by an increase in rate, or, in the case of an embarrassed heart, a sufficient increase in depth may be impossible and an increase in rate must be resorted to.

We are quite ready to admit that observations on total ventilation and rate alone are not without value. For instance, if after giving a drug the rate was found to remain the same and the total ventilation increased, alveolar ventilation must have increased also. If, however, the rate and total ventilation are both increased, the alveolar ventilation might or might not be increased, and the only way to decide the point would be to determine the dead space and calculate the alveolar ventilation. We also wish to emphasize the necessity of studying the metabolism coincidently with alveolar ventilation, for, even though the alveolar ventilation were determined, it would be impossible to tell whether an increase were due to an increased metabolism or to an increased excitability of the center, unless either the carbon dioxid elimination or the alveolar carbon dioxid tension were determined. It is true that, were an increase in alveolar ventilation found and the carbon dioxid tension unchanged, it might be inferred that the metabolism had been increased. It seems more accurate, however, to determine the metabolism directly as a check on the other findings.

The literature contains a large amount of experimental work on the action of drugs on respiration. This work, with a few exceptions, has been done on animals and by far the greater portion is on the

4. Loewy, A.: Zur Kentniss der Erregbarkeit des Athemcentrums, Arch. f. d. ges. Physiol., 1890, xlvii, 601.

effect of depressants, rather than stimulants. Loewy[4] in 1890 studied the effect of various drugs, chiefly depressants, on the respiration in human subjects. He determined the total ventilation and the increase in it produced by definite increases in the expired carbon dioxid. Camphor is the only one of the drugs that he studied with which we have worked. His results are plotted in the form of curves in which the ordinates are the inspired carbon dioxid percentage and the abscissae the total ventilation in a given time unit. With two subjects after 0.5 gm. of camphor he obtained in one instance a slight increase (over normal) in total ventilation to a given rise in carbon dioxid tension of the inspired air, but with another subject the results were practically negative.

In 1892 Wood and Cerna[5] studied the effect of a number of drugs on total ventilation and the respiration rate in dogs. After strychnin there was nearly always an increase in total ventilation. The rate sometimes was increased, and sometimes not. The dosage of strychnin used was from 0.00007 to 0.00019 gm. per kilo body weight, and was sufficient, in most of the experiments, to produce toxic symptoms.

A similar increase in total ventilation, and usually in respiration rate also, was noted after atropin. In the case of both these drugs, when both rate and total ventilation were increased, the alveolar ventilation must have increased, but since we do not know the alveolar carbon dioxid there is no means of knowing whether the increase was due to increased metabolism or increased excitability of the respiratory center.

The same may be said of the work of Impens,[6] who found an increase in total ventilation and rate after the administration of caffein in rabbits. The same author, with camphor and strychnin, obtained negative results.

Biberfeld[7] also made some observations on strychnin in rabbits. The respiration rate and total ventilation alone were determined and the results were somewhat variable, in some cases there being an increase in total ventilation, in others not.

Dreser[8] in 1898 carried out some extensive researches on the effect of the various members of the morphin group in rabbits. The animals breathed through Müller valves and the total ventilation was measured with a meter. The oxygen absorption was determined with a modified

5. Wood, H. C., and Cerna, D.: The Effect of Drugs and Other Agencies upon the Respiratory Movements, Jour. Physiol., 1892, xiii, 870.

6. Impens: Les analeptiques de la respiration, Arch. de pharmacodynam, 1899, vi, 149.

7. Biberfeld: Zur Wirkungsweise des Strychnins auf das Athmungscentrum, Arch. f. d. ges. Physiol., 1904, ciii, 266.

8. Dreser, H.: Ueber die Wirkung einiger Derivate des Morphins auf die Athmung, Arch. f. d. ges. Physiol., 1898, lxxii, 485.

Regnault apparatus. A decrease in both rate and total ventilation was found with these drugs, most marked in the case of heroin. The alveolar ventilation, therefore, must have been decreased and this presumably was due to a depression of the center, because the change was very marked, but again we cannot be certain that it may not have been due, in part at least, to a decrease in metabolism, for the alveolar carbon dioxid was not determined. The consumption of oxygen after codein and heroin in most of the experiments showed a fall, indicating that metabolism probably did decrease; the carbon dioxid elimination unfortunately was not determined.

Cushny[9] in 1913 studied the effect of caffein and strychnin on the depth and rate of respiration, using a modified body plethysmograph and recording tambour. In the case of both these drugs he found the rate increased and the depth slightly decreased. The reaction to carbon dioxid was also tested, and it was found that there was a greater increase in rate after these drugs than before. Here again, not knowing the alveolar carbon dioxid or alveolar ventilation, we are somewhat at a loss to get the real significance of the results obtained.

The present communication is a preliminary one; it is based on a small number of experiments, but the results seem to be sufficiently striking to make it worth while to report them at the present time.

The methods employed were as follows: The subjects were two normal men, both physicians who voluntarily submitted to the investigation. The experiments were done in the morning, before food was taken (except in the case of Experiment 8, in which a cup of coffee had been taken one hour before experiment was begun) in the recumbent position. The observations on respiration were made with Benedict's so-called Universal Respiration Apparatus.[10] By means of this instrument we measured directly the total ventilation, the carbon dioxid output, the oxygen absorption and the rate of the respiration. The apparatus was run for ten-minute periods. The subjects were always kept at rest in the recumbent position for half an hour before the first period was begun and did not leave the couch until the end of the experiment. One, or in some cases two, normal periods were run, the drug was then given, and two to three subsequent periods run. The systolic blood-pressure was taken frequently by means of the Faught mercury apparatus, the figures in the following protocols representing averages of readings just before, just after and during each period. Frequent pulse-counts were made through a long stethoscope strapped

9. Cushny, A. R.: On the Pharmacology of the Respiratory Center, Jour. Pharm. and Exper. Therap., 1913, iv, 363.

10. Benedict, F. G.: Ein Universalrespirationsapparat, Deutsch. Arch. f. klin. Med., 1912, cvii, 156.

to the cardiac area and arranged so that the subject did not know when his pulse was being counted. The figures in the protocols represent averages of three or more counts.

The dead space in the chest was determined for each subject by taking the carbon dioxid tension by the Haldane method and calculating the dead space from this, together with the result of a respiration

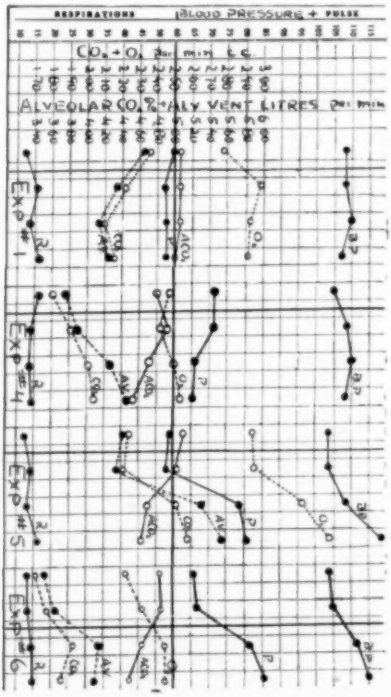

Chart showing diagrammatically Experiment 1 (strychnin), Experiment 4 (caffein), Experiment 5 and Experiment 6 (atropin). The heavy perpendicular line separates periods before, from those after, the administration of the drugs. B. P. = systolic blood-pressure; P = pulse-rate per minute; R = respiration rate per minute; O_2 = oxygen absorbed cubic centimeters; CO_2 = carbon dioxid eliminated, cubic centimeter per minute; ACO_2 = alveolar carbon dioxid per cent.; A. V. = alveolar ventilation liters per minute.

experiment. This was done from several normal periods on the respiration apparatus and Haldane determinations taken on different days, and the results agreeing satisfactorily, the average was used as the value for the dead space in the calculation. The dead space having been found, the alveolar ventilation was obtained by multiplying the dead space by the respiration rate, and subtracting the product from

the total ventilation. The percentage of carbon dioxid in the alveolar air has been calculated with sufficient accuracy for our purposes by dividing the carbon dioxid output per minute by the alveolar ventilation per minute. This has been done for each period and the carbon dioxid percentages given in the protocols were obtained in this manner. The alveolar carbon dioxid has been expressed in percentage rather than as actual tension, because, unless there is a marked change in the barometer, changes in percentage run parallel with those in tensions.

When we began the investigation we believed that the size of the dead space remained constant in any individual. We based this belief on Krogh's[11] recent work in which he found no change in the dead space in a given individual under widely varying conditions, such as extreme muscular work or complete rest. For this reason it did not seem important to make frequent direct determinations of the carbon dioxid tension, and we thought that the calculated values would give us the information we desired. In a second series of experiments now in progress in collaboration with H. L. Higgins of the Carnegie Nutrition Laboratory, however, we have obtained evidence that some drugs may alter the size of the dead space by acting as bronchoconstrictors or dilators, as mentioned in the beginning of this paper. Of the four drugs discussed here, the effect has been found with atropin only. The question of changes in the dead space will be discussed when we publish this second series, in which a larger number of drugs have been studied and frequent direct determinations of the carbon dioxid tension made.

We have to report eight experiments at the present time, two with strychnin, two with caffein, two with atropin and two with camphor. One experiment was done with each of the four drugs on each subject. Experiments without drugs have also been done on both subjects, the results of which were perfectly normal. The protocols of the eight drug experiments are given in full, and in addition, Experiments 1, 4, 5 and 6 are shown diagrammatically on a chart.

We wish to thank Drs. O. F. Montgomery and M. N. Smith-Peterson, who not only acted as subjects but also rendered invaluable assistance at the experiments. We also wish to thank Messrs. T. M. Carpenter and H. L. Higgins of the Nutrition Laboratory for much valuable assistance and advice in the use of the respiration apparatus. The experiments in detail were as follows:

REPORT OF EXPERIMENTS

Experiment 1.—*Strychnin.*—Subject O. F. M. After one normal period and during the first third of the second period, strychnin sulphate, 1/15 grain, was given subcutaneously. The three subsequent periods show practically no

11. Krogh, A., and Lindhard, J.: The Volume of the Dead Space in Breathing, Jour. Physiol., 1913, xlvii, 30.

change in the alveolar carbon dioxid tension and a fall in the alveolar ventilation which is strictly parallel with a fall in the carbon dioxid eliminated per minute; a slight rise in the oxygen per minute also occurs. The systolic blood-pressure shows very little change and the pulse a very slight drop; the respiration rate is practically unaltered.

EXPERIMENT 2.—*Strychnin.*—Subject M. N. S-P. In this experiment the dose of strychnin and the method and time of administration were the same as in Experiment 1. We find again a steady fall in the carbon dioxid elimination with a slight rise in the oxygen as in the case of Experiment 1. The alveolar carbon dioxid rises very slightly, and the alveolar ventilation falls somewhat more than in Experiment 1, which is explained by the slight rise in the alveolar carbon dioxid tension. The systolic blood-pressure shows a very slight rise, the pulse a very slight drop, and the respiration rate is unchanged.

EXPERIMENT 3.—*Caffein.*—Subject O. F. M. In this experiment caffein sodium salicylate, 5 grains, was given subcutaneously during the first third of the second period and repeated during the first third of the third period. The metabolism shows a definite rise during the second period, and again falls during the third and fourth. The alveolar carbon dioxid tension shows first a rise, then a fall to slightly below the starting-point. Alveolar ventilation shows some rise. Blood-pressure, pulse and respiration are but little affected.

EXPERIMENT 4.—*Caffein.*—Subject M. N. S-P. The results are much more striking. Three grains of caffein sodium salicylate were given during the first third of the second period and repeated during the first third of the third period. The metabolism shows a marked rise, the alveolar carbon dioxid tension a marked drop, and the alveolar ventilation a rise which is proportionately greater than the rise in carbon dioxid per minute. Respiration rate is unchanged. Blood-pressure shows a slight rise and the pulse a slight fall.

EXPERIMENT 5.—*Atropin.*—Subject O. F. M. After a normal period, atropin, 1/50 grain was given during the second period and repeated during the third period. Dilatation of the pupils, dryness of the throat, dizziness and increase in pulse-rate all occurred, showing that we had given sufficient to produce typical atropin action. The experiment shows a marked rise in metabolism, in blood-pressure, and in pulse-rate, also a definite fall in alveolar carbon dioxid and a rise in alveolar ventilation which is proportionately greater than the rise in carbon dioxid eliminated per minute. Respiration rate shows a very slight rise.

EXPERIMENT 6.—*Atropin.*—Subject M. N. S-P. The results of this experiment confirm those of Experiment 5. Here only 1/50 grain of atropin was given between the second and third periods. Pulse and blood-pressure show a marked rise; so also does the metabolism. Alveolar carbon dioxid tension shows a definite drop and alveolar ventilation a rise proportionately greater than the rise in carbon dioxid per minute.

EXPERIMENT 7.—*Camphor.*—Subject O. F. M. Camphor, 4 grains, given intramuscularly during the third, and 4½ grains during the first third of the fourth period. Metabolism shows a very slight rise followed by a fall. Alveolar carbon dioxid shows a slight rise, and the alveolar ventilation runs parallel with the carbon dioxid elimination per minute. Blood-pressure and respiration rate show a slight fall; pulse remains nearly level.

EXPERIMENT 8.—*Camphor.*—M. N. S.-P. Here only 4 grains of camphor were given between the second and third period. The metabolism remains normal, the alveolar carbon dioxid shows a moderate drop and the alveolar ventilation a corresponding rise; blood-pressure a slight rise, pulse a definite fall, respiration rate unchanged.

EXPERIMENT 1.—Subject O. F. M. Effect of Strychnin *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
10:44 a.m.	236	279	0.85	6.96	4.67	5.06	12.1	60.0	108
11:17 a.m.	221	299	0.74	7.23	4.37	5.06	15.1	55.5	108
11:40 a.m.	210	292	0.72	6.71	4.16	5.05	13.5	56.0	110
12:12 p.m.	213	291	0.73	7.38	4.26	5.00	16.5	55.5	106

* Strychnin sulphate given subcutaneously, 1/15 grain, during first third of second period.

EXPERIMENT 2.—Subject M. N. S-P. Effect of Strychnin *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
10:21 a.m.	192	234	0.82	7.07	3.93	4.89	14.5	72.0	108
10:53 a.m.	189	244	0.77	7.00	3.82	4.95	14.7	71.0	108
11:16 a.m.	180	241	0.75	6.86	3.58	5.03	15.2	67.0	111
11:45 a.m.	184	246	0.75	6.98	3.59	5.12	15.7	69.0	112

* Strychnin sulphate given subcutaneously, 1/15 grain, during second minute of second period.

EXPERIMENT 3.—Subject O. F. M. Effect of Caffein *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
11:00 a.m.	219	275	0.80	6.94	4.63	4.74	12.2	55.0	105
11:41 a.m.	245	316	0.77	7.56	4.86	5.04	14.3	51.5	105
12:17 p.m.	230	300	0.77	7.71	4.95	4.64	14.6	51.5	104
12:44 p.m.	224	309	0.72	7.43	4.82	4.65	13.8	49.5	104

* Caffein sodium salicylate given subcutaneously, 5 grains, during first third of second period and 5 grains during first third of third period.

EXPERIMENT 4.—Subject M. N. S-P. Effect of Caffein *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
10:47 a.m.	180	248	0.73	7.25	3.75	4.80	16.2	72.0	105
11:05 a.m.	192	241	0.80	7.06	3.88	4.95	14.7	72.0	108
11:30 a.m.	201	250	0.80	7.38	4.25	4.72	14.5	66.0	110
11:49 a.m.	205	257	0.80	7.73	4.51	4.54	14.9	65.5	108

* Caffein sodium salicylate given subcutaneously, 3 grains, during first third of second period and 3 grains during first third of third period.

EXPERIMENT 5.—Subject O. F. M. Effect of Atropin *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
8:58 a.m.	226	295	0.77	6.80	4.42	5.11	12.6	59.0	104
9:22 a.m.	221	296	0.75	7.16	4.38	5.05	14.7	57.0	104
10:15 a.m.	253	323	0.78	7.87	5.35	4.73	13.3	78.0	108
10:38 a.m.	258	339	0.76	8.74	5.58	4.62	16.7	80.5	118

* Atropin sulphate given subcutaneously, 1/50 grain, during first third of second period and 1/50 grain in middle of third period.

EXPERIMENT 6.—Subject M. N. S-P. Effect of Atropin *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
2:27 p.m.	171	222	0.77	658	353	4.85	14.1	66.0	104
2:53 p.m.	178	233	0.77	674	366	4.87	14.2	67.0	105
3:45 p.m.	194	246	0.79	738	416	4.65	14.9	82.0	112
4:15 p.m.	186	246	0.76	735	411	4.52	15.0	87.0	115

* Atropin sulphate given subcutaneously, 1/50 grain, between second and third periods (3:17 p. m.).

EXPERIMENT 7.—Subject O. F. M. Effect of Camphor *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
11:01 a.m.	225	285	0.79	6.96	4.48	5.01	13.1	58.0	115
11:28 a.m.	220	278	0.79	7.13	4.09	5.39	16.1	56.0	112
12:09 p.m.	227	304	0.75	6.92	4.35	5.21	13.6	55.0	109
12:34 p.m.	206	277	0.75	6.36	4.04	5.11	12.3	54.5	109

* Camphor (in oil) given intramuscularly, 4 grains, during first third of third period and 4½ grains during first third of fourth period.

EXPERIMENT 8.—Subject M. N. S-P. Effect of Camphor *

Time	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Total Ventilation per Min., Liters	Alveolar Ventilation per Min., Liters	Alveolar CO_2 Per Cent.	Average Respiration Rate per Min.	Average Pulse-Rate per Min.	Average Systolic Blood-Pressure
9:37 a. m.	208	240	0.87	7.41	4.08	5.09	15.4	66.5	109
9:56 a. m.	188	239	0.79	7.00	3.74	5.03	15.1	64.0	108
10:50 a. m.	188	237	0.79	7.23	3.90	4.82	15.4	59.0	112
11:35 a. m.	189	238	0.79	7.15	3.95	4.79	14.8	58.0	110

* Camphor (in oil) 4 grains given between second and third periods.

DISCUSSION OF RESULTS

The results obtained with strychnin are clearly negative except possibly for a slight increase in metabolism. The alveolar carbon dioxid in one instance remained constant, and in the other showed a slight rise. The effect on circulation and respiration rate is esssentially negative. It would seem reasonable to conclude that in the case of these two normal individuals strychnin was without recognizable effect on the respiratory center, or the circulation, and also that the general character of respiration is unchanged; it may have slightly increased their metabolism.

Both experiments with caffein show a definite although not very great rise in metabolism. One shows a marked stimulation of the respiratory center as indicated by a fall in the carbon dioxid tension and a rise in the alveolar ventilation; the other shows the same thing, but to a less marked extent.

The experiments with atropin are in perfect agreement and show a definite rise in metabolism, a marked fall in the alveolar carbon dioxid, and a rise in alveolar ventilation. We thought at first that the latter two effects were due to a stimulation of the respiratory center, and they probably are in part, but as we mentioned before, subsequent experiments (to be published later) have indicated that this may also, in part, be due to a change in the size of the dead space.

The results obtained with camphor show no constant effects. In one experiment there was a slight fall in carbon dioxid tension, suggesting that there may have been some stimulation of the center, but in the other experiment there was none. Circulation and respiration rate are essentially unaltered. Metabolism shows a temporary rise in one case, and no effect in the other.

The objection may be raised that these drugs may act differently on sick and on normal individuals. This is highly probable, and we intend to work with pathologic cases later. The effect of the drugs on normal persons, however, should be established first, and the effect on normal men is of even more importance than that on lower animals, which is what has chiefly been studied.

A single observation has been made with atropin in marked Cheyne-Stokes breathing, occurring in a case of cerebral hemorrhage. Assuming that the Cheyne-Stokes breathing may have been due to a decreased excitability of the respiratory center, it seemed reasonable to give a drug which we believed stimulated this center. Enough atropin was given to cause marked increase in pulse-rate; the respiration was recorded by a pneumograph and showed absolutely no change after the administration of atropin. We were unable to obtain the alveolar carbon dioxid tension, as the patient was in coma, and Boothby and

Peabody's[12] pharyngeal tube method for obtaining samples of alveolar air had not been published at the time the case was in the hospital.

In this connection the results of Parkinson and Rowlands[13] studying the effect of strychnin in cases of cardiac decompensation are of interest. These authors found no change in respiratory rate after doses of $\frac{1}{15}$ grain of strychnin. They also were unable to observe any alteration in depth, but no means for recording this accurately were employed. In five cases of Cheyne-Stokes breathing absolutely no change in the respiratory curve was found after strychnin.

CONCLUSIONS

We think the following conclusions are justified:

1. Strychnin: No action on the respiratory center or circulation, possibly an increase in metabolism.

2. Caffein: Stimulation of respiratory center, moderate increase in metabolism, no effect on circulation.

3. Atropin: Marked increase in metabolism, in doses large enough to cause the classical action on the circulation. Marked drop in the calculated values for alveolar carbon dioxid and rise in alveolar ventilation. Whether these latter effects are due to stimulation of the respiratory center or to changes in the dead space is not clear at the present writing.

4. Camphor: The results not agreeing, no conclusions are justifiable.

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12. Boothby, W. M., and Peabody, F. W.: A Comparison of Methods for Obtaining Alveolar Air, THE ARCHIVES INT. MED., 1914, xiii, 497.

13. Parkinson, J., and Rowlands, R. A.: Strychnin in Heart Failure, Quart. Jour. Med., 1913, vii, 42.

SOME CONSIDERATIONS ON THE PHYSIOLOGY OF THE OTIC LABYRINTH *

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The philosopher's statement, now more than a century old, that there is nothing in the mind that has not come in through the senses, might be applied to motion in general. Certainly, so far as those movements due to the central nervous system are concerned, we may say that there are extremely few motions that have not had their antecedent afferent impulses. The modern conception of the nervous system regards it as a mechanism in which afferent impulses, arising in the various kinds of peripheral receptors or sensory endings are gathered up into a definite body of sensory impulses, and somewhere in their course, are summed or integrated to a definite orderly motor response.

For example, when a child is learning to write, and is copying a simple figure, afferent impulses are passing in from various peripheral sources, not from the eye alone, but also from the skin, and the muscles which feel and grasp the pencil, and from other sources. The actual movements of the pencil in the fingers are in response to all these impulses, some of which make their way to the cerebrum directly, and others, particularly those which deal with the "unconscious sensation" of the muscles, pursue an indirect path through the cerebellum. But all these afferent impulses, from whatever source or over whatever path, must be associated or added together and harmonized — integrated — within the brain before the fingers can be moved adequately.

The labyrinth of the ear is a circumscribed, definitely located peripheral sense organ, and one task of modern physiology is to inquire into (1) the modes of stimulation of the particular forms of sensory endings which are found in the labyrinth, (2) the effect of the normal afferent impulses from the labyrinth on the normal motor response of the animal, and (3) the particular variations in this motor response occasioned by afferent impulses of unusual violence, e. g., those arising from artificial stimulation or from pathological processes within the ear, or by total lack of such afferent impulses following experimental or pathological loss of the labyrinth.

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* Based on a paper read before the Section on Neurology of the New York Academy of Medicine, Feb. 11, 1913.

Obviously, the detailed consideration of all these matters would transcend the limits of such a paper as the one we now purpose to present, and we will consider, therefore, certain salient points which have impressed themselves on us in the course of a long and rather detailed study of the subject.[1]

Exact experimental work on the semicircular canals began with Flourens in 1828, although other investigators, notably Purkinje, had stimulated the canals in various ways without knowing exactly with what structures they were dealing. Flourens, while experimenting on pigeons, noticed that after removal of one canal, movements of the head occurred in the plane of the destroyed canal, or, as it is sometimes expressed, about an axis perpendicular to the plane of the destroyed canal. Flourens' work has been repeated by many subsequent observers, and the results may now be regarded as firmly established. These specific effects of experimental lesions of the semicircular canals are not due, as some have supposed, to accidental injury to the cerebellum, or to the extension of inflammatory processes to it. Nor does experimental removal of the cerebellum, without injury to the labyrinth or to the vestibular nerves, in our experience on mammals result in exactly the same motor disturbances as elimination of the labyrinth.

In pigeons, removal of one labyrinth is followed in ten to fourteen days by torsion of the head. But removal of the cerebellum in part or wholly, is not followed by such torsion, but by tremors. Removal of the cerebellum and then removal of the labyrinth is followed immediately by the onset of torsion, and the less the amount of cerebellar tissue removed, the greater the delay in the onset of the torsion. This indicates that in pigeons, so far as torsion is concerned, there is something in the cerebellum which resists the onset of torsion, and removal of the cerebellum does not impede its onset. In other words, torsion is essentially an extracerebellar phenomenon. This is quite in keeping with our observations on mammals, with reference to torsion and nystagmus as well.[1]

Removal of the cerebellum in the pigeon, without injury to the labyrinth is, as Lange[2] points out, a matter of some difficulty. Obviously, unless we can get lesions, restricted to the labyrinth without injury to the cerebellum on the one hand, and lesion of the cerebellum alone without involvement of the labyrinth or vestibular tract on the other, we can get no clear or exact picture of the effects of such lesions, and hence no exact basis for a differential diagnosis of pathological lesions of these two mechanisms.

1. Wilson and Pike: Philosophical Trans. Royal Soc., London, Series B, 1912, cciii, 127.
2. Lange: Arch. f. d. ges. Physiol., 1891, l, 615.

Experimental elimination of the labyrinth in the pigeon and many other animals has been accomplished (1) by anatomical removal of the labyrinth or division of the vestibular nerve, and (2) by anesthetizing the labyrinth with cocain. *Stimulation* of the labyrinth has been done by electrical currents, temperature, ice, hot and cold water, hot wire, etc., mechanical pressure, withdrawal of water by crystallin substances applied to the membranous labyrinth, and rotation of the body and particularly of the head, about an axis perpendicular to the plane of some one set of canals. The various forms of stimuli may be classified according to their effects as strong or weak. The stronger stimuli, e. g., closure of the electrical current when the cathode or negative pole is over the labyrinth, hot water, in certain positions of the head in space, strong pressure on the endings of the vestibular nerve, or a fluid current set up either by mechanical pressure on the canal or by placing a crystal of cocain on the horizontal canal in such a position that the *current* is toward the ampulla, cause a movement of the head and eyes in the plane of the canal and *away* from the stimulated side. More moderate stimuli, e. g., the closure of the electrical current when the anode is over the labyrinth, cold water or ice, again with due reference to the position of the head, and withdrawal of water in such a way that the current is away from the ampulla (horizontal canal), cause movement of the head and eyes in the plane of the stimulated canal toward the stimulated side.

The extremely slow currents set up by the slow withdrawal of water from the canals must not be confused with the strongly flowing currents sometimes supposed to be set up in the semicircular canals by change of aspect of the head in space or by irrigation of the external auditory meatus with hot and cold water.

Much discussion has arisen as to whether the effects of unilateral anatomical removal are due to simple absence of one labyrinth, or to irritation of the nerve endings and nerve trunk in the operation wounds. We may safely say that irritation plays but little part in the effects of anatomical removal since (1) the same results are obtained when the labyrinth is anesthetized with cocain, and (2) the results of irritation, if any be present, are the same as those observed after application of the weaker stimuli to the labyrinth, and (3) the results of removal of the second labyrinth after an interval are much less severe than those observed after removal of the first labyrinth. The results are, in the main, due to the unbalanced action of the intact labyrinth.

Without at this time going into a detailed review of the evidence on which the statement rests, we may say that the effects of elimination of the left labyrinth, either by anatomical removal or anesthesia by

cocain, are the same as those following electrical stimulation of the labyrinth with the anode over the mastoid fossa, by the application of cold water to the ear, or by rotation to the right. We may, then, consider at this time, the specific results of experimental lesions of the labyrinth, of anesthesia, of electrical and thermal stimulation and of rotation, and afterward consider certain theories of the action of the labyrinth.

In point of historical development, the first most important work goes back to Purkinje whose laws of rotation vertigo, as they are now called, were worked out before Flourens did his experimental removals. Although Purkinje's observations were correct in every essential particular, he did not attribute the results to the semicircular canals, but supposed that in rotation the brain exerted traction on certain cranial nerves because it lagged behind the skull in starting or stopping. We may give these laws of rotation vertigo in detail.

We should distinguish between the period during which rotation actually occurs—the rotation period proper—and the period beginning immediately after the cessation of rotation—known as the postrotatory period. If one stands erect, or sits erect in a chair, and rotates, say to the right, objects may apparently move to the left and one has a sensation of real movement to the right. Shutting the eyes excludes the apparent movement of external objects, but does not affect the sensation of movement of one's own body. If one stands erect and rotates about a vertical axis for some minutes and then stops, surrounding objects still appear to move around and vertigo may be present in the postrotatory period. The direction of the apparent motion of oneself depends on the directions of the preceding real motion and is always opposite in direction. If one bends the head forward 90 degrees and then rotates, the apparent movement during the postrotatory period is about a vertical axis. But if, after again bending the head forward and rotating, the head is raised to an erect position during the post rotatory period, the apparent movement is no longer about a vertical but about a horizontal axis. Objects will seem to rise on one side and fall on the other. The axis about which apparent movement occurs is always the axis of the head about which the preceding real rotation occurred. Hitzig, in his classical paper, gave the first clear and accurate account of the results of electrical stimulation of the labyrinth—galvanic vertigo—and showed that these results fall into line with those of rotation vertigo. When the cathode is placed over the left fossa mastoidea and the anode over the muscles of the neck, the eyes move slowly to the right and quickly back to the left. The subject may get the impression of apparent movement of his own body to the left; the apparent movement of external objects is frequently to the left, but varies with the

individual. Closing the eyes abolishes the impression of apparent movement of external objects, but does not abolish the sensation of apparent movement of one's own body. As Hitzig expressed the relation between stimulating electrode and direction of eye movement, the quick movement of the eyes is in the direction of flow of the electrical current, i. e., in the case just cited, toward the cathode.

Hitzig[3] was among the first to stimulate the labyrinth with cold, although he did not know at the time that it was the labyrinth he was stimulating. Bornhardt,[4] a few years later, employed the direct application of heat and cold to the labyrinth as stimulating agents. Goltz[5] referred to the disturbance of equilibrium and the eye movements following incautious irrigation of the external auditory meatus, especially when the tympanic membrane was ruptured, as being common knowledge in his day, and attributed the effects to stimulation of the semicircular canals and the labyrinth generally by the water. From these early beginnings, there has grown up the caloric test as applied in clinical practice of the present day, largely due to the work of Bárány.

Anatomical removal of the labyrinth in mammals, e. g., dogs and monkeys, is accompanied by certain characteristic phenomena. Certain of these are acute, lasting but a few days, while others persist as long as the animal lives. If one labyrinth only is destroyed, there is a slow movement of the eyes toward the injured side, and a quick return jerk to the median position. This nystagmus persists but a few days, and then wholly ceases, the eyes being then normal in position and capability for movement. In lower forms, such as the dog-fish[6] and turtle,[7] the eyes are permanently deviated toward the injured side, and there is no nystagmus.

Although the eyes in mammals appear to come back to the normal position in a few days, we have repeatedly observed that if the animal be placed in an abnormal posture, e. g., on its back, the symmetrical position of the eyes is altered and there will be observed a marked ventral deviation of the eye on the side of the lesion. This persists for weeks. The animal's head is permanently turned toward the injured side, and, in the early days of the postoperative period, the animal falls or rolls to the injured side. Later the animal becomes able to walk without falling, but turns toward the injured side so that it goes in a circle. In a few days more, it is able to walk a straight line, even when

3. Hitzig: Arch. f. Anat. u. Physiol., 1871, p. 771.
4. Bornhardt: Arch. f. d. ges. Physiol., 1876, xii, 471.
5. Goltz: Arch. f. d. ges. Physiol., 1870, iii, 192.
6. Jour. Physiol., 1894, xv, 311; 1895, xvii, 192.
7. Wilson and Pike: Proc. Soc. Exper. Biol. and Med., 1913, xi, 52.

its eyes are covered. The transitory falling over of the animal to the side of the lesion and the persistent deviation of the head is, we believe, due to the over activity of the intact labyrinth, whereby the muscles, chiefly the extensors on the intact side, are acting more effectively.

If both labyrinths are removed at one time, there is nystagmus as before, but it is irregular in character and does not persist as long as after unilateral removal. There is no torsion of the head to one side or the other, or at most, a comparatively slight inclination. The animal refuses to stand, but lies with head and feet outstretched and paws clutching the floor. If the head is raised voluntarily, there are coarse swaying movements reminding one of the swaying of a reptilian head. Food is not accurately grasped with the jaws. In attempting to take food, the nose is thrust to one side, above or below the desired object, only rarely touching the object squarely. A turtle deprived of both labyrinths may die of starvation because of its inability to seize food. In the dog and cat, the swaying movements cease in two weeks or less, and the accuracy of grasp returns. Gradually, also, the cat or dog learns to walk, falling to one side or the other in the first attempts, and turning now to one side, now to the other in its efforts to cross a room. Finally, all these symptoms disappear, and it would be difficult for one to detect any motor disturbance in a dog with eyes unbandaged in walking across grass or a level floor, or in taking food.

The eye movements are of particular interest in connection with stimulation or removal of the labyrinth, and we may inquire into them in detail.

In all animals so far experimented on there is a slow movement of the eyes toward the injured labyrinth or toward the labyrinth to which the weaker stimulus is applied. In rotation, the eyes lag behind, going slowly to the side opposite to that toward which the body is rotated. In the postrotatory period the slow movement of the eyes changes and acquires the same direction as the preceding real rotation. The typical oscillatory movement of the eyes, alternately slow in one direction and quick in the opposite direction, is seen best in mammals. So far as our observation or knowledge goes, this is a characteristic type of nystagmus not seen in experimental lesions of the cerebellum or of any other portion of the central nervous system so long as the vestibular tract is intact. The slow deviation alone is seen in certain of the lower forms. We have found that the slow deviation alone is seen in decerebrated or partially anesthetized animals. Nystagmus in its characteristic form occurs only in those animals which have recovered to a considerable extent from the anesthetic, or in which the optic thalamus with the corpora striata and a considerable portion of the cerebral hemispheres remained. Some part of the mechanism which produces nystagmus

must, therefore, be anterior to the corpora quadrigemina. The exact paths concerned will be reported on later.

Bartels, basing his views partly on the afferent nerve endings recently described in the eye muscles by Sherrington and his pupils, and partly on rotation experiments on infants, concludes that the quick return jerk of the eyes in labyrinthine nystagmus is a reflex dependent on some mechanism, probably cortical, but certainly cerebral. Bartels is not inclined to accept Bárány's view of a hypothetical *Blick-centrum* as the cause of nystagmus. Bartels found that in the first seven days of post partum life, rotation nystagmus was not obtainable. Later, it is obtainable when the child is awake, but not during sleep. Prematurely-born infants do not exhibit rotation nystagmus for some time after birth. An infant born at the end of seven months, uterine life does not show rotation nystagmus in the early postpartum period, although anatomically, the semicircular canals are fairly well developed at the end of three months. The time of appearance of rotation nystagmus apparently depends more on the period elapsing after birth than on the absolute length of gestation.

We agree in the main with Bartels' idea of the mechanism of labyrinthine nystagmus, and have published additional evidence of their essential correctness and extended them considerably.

Clinicians and laboratory workers alike have been impressed with the quick phase of nystagmus, and the direction of nystagmus is usually given as the direction of the quick movement. In so doing, all have fixed attention on the mechanism which brings about the return of the eye to the normal position, and not on the lesion which causes the eye to deviate from its normal position. But the cause of the deviation from the normal position is the very thing which the clinician is most anxious to discover. If the experimenter has anything definite to say to the clinician, it is this one thing, that the cause of the slow deviation in labyrinthine nystagmus lies in the labyrinth or in the vestibular tract, and that the slow component of nystagmus is the one which it is most important to observe. The cause of the ocular deviation from the normal position may lie in other parts of the central nervous system than the labyrinth or the vestibular tract, and each may bring about the deviation in a particular way. The manner of return to normal is more likely to be uniform. Involvement of the labyrinth or the vestibular tract always, in experimental procedures at least, produces a relatively slow, wide deviation, in which both eyes move together, and we may repeat that labyrinthine nystagmus is characterized by these alternately slow and rapid movements. As at present used, nystagmus is an indefinite term, covering various types of ocular movements arising from lesions in diverse parts of the nervous system,

and a more careful distinction of the different types of eye movement is greatly to be desired.

After the subsidence of the symptoms of the acute stage, certain other permanent defects are observable.

If but one labyrinth has been removed, there is a permanent torsion of the head to the injured side, and there may be a leaning, particularly of the anterior part of the body, to this side. This torsion of the head is much more marked in animals than in the human subject. In the latter, the torsion may be negligible. If both labyrinths have been removed, either at one sitting or at intervals, there is no marked torsion of the head or inclination of the body to one side. With eyes bandaged, the animal is unable to walk in a straight line, but goes now to one side, now to the other, or turns helplessly in a small circle. Ascending stairs offers no particular difficulty, but descending stairs usually results in a headlong fall. Jumping down from even a moderate height results in falling in a heap on the floor. An animal with one labyrinth intact walks in a straight line when blindfolded, ascends or descends stairs and jumps up or down without difficulty. In neither animal is there any loss of the sense of position of the muscles, so far as can be made out. The drop reflex — the thrusting out of the hind feet and legs when the animal is held vertically, head up, and rather rapidly lowered with the hands — is greatly depressed or wholly absent on the side of labyrinthine injury. In no case can any confusion concerning the relation of the parts of the body to each other, or to the body as a whole, be made out. The animal's mistakes and failures concern his relation to external objects or his orientation in space.

Such briefly and in general are the results of labyrinthine removal. Various theories have been put forward to explain these defects. We may mention certain of them. The first clear conception is due to Goltz, who pointed out that, in the labyrinth and its central connections we had, first, a peripheral sense organ in the semicircular canals and the other portions of the otic labyrinth; second, a centripetal path from this end organ to the central mechanism, and finally certain centrifugal paths from the central mechanism to the muscles, through which the motor response is brought about. The function of the labyrinth is, therefore, a reflex one.

Goltz, however, supposed that the end organs were stimulated by changes in hydrostatic pressure in the labyrinth as the animal moved its head about in space. Although certain remnants of this hydrostatic theory still survive and are likely to survive for some time to come, it has been largely superseded by the kinetic theory of Mach, Breuer and Brown, particularly with reference to the semicircular canals. As Brown expressed it, on the basis of the hydrostatic theory, and static

theories in general, the labyrinth is regarded as an organ which gives information of the aspect of the head in space. In the kinetic theory, the labyrinth, and especially the semicircular canals, are regarded as an organ which gives information of the change of aspect of the head in space. The distinction is important, for, in response to rapid changes of aspect of the head in space, prompt and rapid motor reactions are necessary to preserve equilibrium or to break a fall. There is no other sense organ in the body which will give this information quite so efficiently as the labyrinth, and hence, there is always a certain amount of permanent deficiency of motor response after total loss of the labyrinths.

Breuer's original idea was that because of its inertia, the fluid in the canals lagged behind when the head was moved in any plane, and the sensory endings in the labyrinth were stimulated by fluid currents. Mach objected to the currents, arguing that from the point of view of experimental physics, currents were impossible in such fine tubes as the semicircular canals; the effective stimulus must be, therefore, a change in pressure in particular regions of the labyrinth, since the fluid would lag behind sufficiently to cause a change in pressure. Breuer and Brown accepted Mach's modifications of the original theory, and it is generally held to-day that changes in fluid pressure, not fluid current, are the effective or adequate stimuli for the sensory endings in the labyrinth. So far as we can see, it is not necessary to assume the existence of actual currents for the explanation of any known response to stimulation of the labyrinth.

Brown showed that the six canals might be divided into three pairs, each pair lying in a plane at right angles to the planes of the other two pairs. Lee showed that each canal in a given pair had two functions, a principal and a subordinate function; and that the subordinate function of each canal of a pair reinforces the principal function of the other canal. As an illustration of this point we have Breuer's statement that, in the horizontal canals, change of pressure from canal to ampulla is a stronger stimulus than change of pressure from ampulla to canal.

Time does not permit a consideration of some of the *"Streitfragen"* of labyrinthine physiology. It may be shown that, under certain conditions, the labyrinth exerts an influence on the state of contraction of certain of the muscles of the limbs. How great this influence is under normal conditions is a matter of conjecture. Again, Stefani's idea that the labyrinth exerted its effect mainly over paths passing through the cerebellum is open to question in part at least. Certainly, typical labyrinthine nystagmus may be induced in a dog after complete ablation of the cerebellum.

Our results are more in line with Luciani's. We believe that while the labyrinthine reaction is primarily a direct reflex effect through the extracerebellar structures, yet the connection with the cerebellum is such that in higher forms at least, the labyrinthine reactions are influenced by the cerebellum.

Finally, the path which labyrinthine impulses follow in going to the cerebrum, or in what part of the cerebral cortex the end stations lie, will be dealt with in a subsequent paper. That labyrinthine impulses do reach the cerebrum is scarcely to be doubted.

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